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SKIN DISEASES NUTRITION AND METABOLISM

BY

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This book is affectionately dedicated

to my wife,

DR. JOSEPHA URBACH

Preface

THE skin is an integral part of the organism. Many diseases of the skin are the direct result of metabolic or nutritional distubances, or of functional or anatomic diseases of internal organs, particularly the gastrointestinal tract, the liver, the pancreas, the endocrine glands, and the nervous system. On the other hand, certain inflammatory processes of the skin due to infection or to chemical irritation may give rise to hepatic, digestive, and other visceral disturbances; and dermatoses and internal disorders may occasionally constitute concomitant expressions of some underlying systemic disease. In this treatise we endeavor to present the first comprehensive survey of the interrelationship between dermatology and internal medicine with particular reference to the nutritional, biochemical, and metabolic aspects.

The science of nutrition has thrown new light on the pathogenesis of a host of skin diseases and has provided effective weapons against many of them. The large section on avitaminotic dermatoses in this volume is testimony therefor. Moreover, the great advances that have been made in the field of biochemistry in recent years have revolutionized dermatologic thinking and therapy. One need only recall the rather recent discovery that certain cutaneous manifestations are due to disturbances of the carbohydrate, lipid, protein, water, or mineral metabolism. We are only now beginning to sense the true importance of cellular disturbances, notably those due to some interference with the process of biologic oxidation and with other enzymatic functions, for example, in the pathogenesis of certain avitaminotic skin diseases. The next few years will, without question, see a vast expansion of our understanding of these relationships.

Although many advances lie in the future, we feel that the time is ripe for a full presentation of the influence of nutrition on the healthy and diseased skin, including the effect of the diet on the biochemistry and metabolism of cutaneous tissue.

While in modern medicine nutritional therapy constitutes an important part of the entire therapeutic approach, dietary measures for the treatment of dermatoses have not been accorded due recognition by dermatologists and internists. This may perhaps be explained by the fact that no book devoted to the dietotherapy of skin diseases exists. The present volume aims to fill this need. We have gathered most of the pertinent information scattered throughout the literature and critically weighed the numerous statements and claims. While the writer has endeavored to present opposing views on controversial questions impartially, he has taken a personal stand and expressed his own opinion wherever necessary, on the basis of twenty-seven years of scientific and practical experience in this field.

There are six modes of action in which dietary regulation in the treatment of cutaneous diseases may be effective: (1) causative, notably in the dermatoses due to metabolic disorders, such as diabetes or gout, or due to gastrointestinal diseases; (2) supplementary, as in vitamin deficiencies; (3) eliminative, as in the withdrawal of the offending food from the diet in allergic dermatoses, and in carotenoderma; (4) biochemical, as in the effort to influence the chemistry of the skin and thereby the cutaneous reactivity, e.g., the use of a salt-poor diet in the treatment of lupus vulgaris; (5) alterative, as in the alteration or *Umstimmung* therapy, in order to achieve an *ictus therapeuticus* by a metabolic thrust, e.g., by radically dissimilar diets used in rapid succession; and (6) supportive, as in the improvement of the patient's general nutritional state through the correction of undernutrition or the reduction of obesity.

From this it can be seen that the influence of nutrition on the skin can be both prophylactic and therapeutic. While dietotherapy is the only effective method of treatment for certain skin diseases, there are, however, many cutaneous disorders in which other measures, internal and external, must be employed in addition to dietary regulation to obtain the best results.

This book is divided into five parts. Part One is devoted to a discussion of the biochemistry of the skin, based in large part on original work by the author, and to a detailed consideration of the influence of the diet on the metabolism of the skin, with particular emphasis on the effects of the various dietary constituents. In order to facilitate dietotherapy of skin diseases numerous dietary tables with the sample menus and directions for dietary treatment are included in this section. Part Two presents a discussion of dermatoses due to malnutrition, with special reference to vitamin deficiencies, and those due to food allergy. For diagnostic and therapeutic purposes alike, the writer prefers the Propeptan method in the treatment of food allergy and therefore discusses this method in some detail. Part Three deals with the influence of diseases of the gastrointestinal tract, liver, and pancreas on the skin, and vice versa. In Part Four the practical application of the dietary therapy of the dermatoses is presented in detail. The efficacy of dietotherapy is documented by numerous photographs and case histories. Part Five consists of nutritional tables designed to help the physician adapt the various types of diets to the quantitative and qualitative needs of the individual.

A bibliography of more than 1,300 references, in the form of footnotes, is included in order to facilitate the work of students of cutaneous diseases and nutrition.

The author is well aware of the fact that the present treatise constitutes nothing more than a modest beginning and that nutritional science will, in the not too distant future, make additional important strides which will further elucidate the pathogenesis of dermatoses and aid in their treatment. It was the writer's intention to provide the foundation for a scientific nutritional therapy of diseases of the skin and its appendages and at the same time to present a practical guide for the physician.

ERICH URBACH

Philadelphia
March, 1946

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Introduction

Nutritional therapy is currently of very special interest to the medical profession, owing, in great part, to the political, economic, and social repercussions of World Wars I and II. However, the use of diet in the treatment of disease is by no means new. Whoever would undertake to write a comprehensive history of the subject would find himself obliged, here, as in so many branches of medicine, to go all the way back to Hippocrates. Moreover, to mention only a few names from the classical medical annals of antiquity, Celsus, Galen, and Aretaeus also prescribed specific dietaries for the treatment of certain diseases. The work of Thessalus of Tralles is especially noteworthy. He endeavored to deal with certain pathological processes by means of sudden and drastic changes in the character of the diet from one extreme to the other, using the term "metasyncrisis" to designate this therapeutic approach. The well-known *umstimmung* therapy of the modern German school, for which the present writer introduced the term "alteration therapy" (see p. 124), is nothing more nor less than the metasyncrisis of Thessalus. It is also interesting to note the passage in the Bible, in the Book of Daniel, which specifically suggests a ten-day trial to determine whether a diet consisting exclusively of vegetables and plain water is better than feasting at the royal board. The simpler diet was found to be more beneficial in this "metabolic experiment."

In later periods of medical science the question of nutritional therapy played a less dominant role. Not physicians, but philosophers and reformers, such as Jean Jacques Rousseau, in France, and above all Benjamin Franklin, in America, became the champions of treatment by means of a vegetarian diet. In England the vegetarian movement was given considerable impetus by J. Newton, whose book *Return to Nature or Defense of Vegetable Regime* appeared in 1811; and, in America, Sylvester Graham was the leader of a movement which advocated a diet of nothing but coarse bread (graham bread), fruit, nuts, and water.

We feel that it is well worth presenting these brief introductory remarks before taking up the history of nutritional therapy of skin diseases. Hippocrates, long ago, had recognized the fact that fasting has a beneficial effect on the healing of wounds, which is especially interesting when viewed in the light of the successes achieved by our contemporaries, Sauerbruch and Herrmannsdorfer, with acidotic diets in wound dealing; for it is well-known that prolonged fasting creates a state of acidosis in the organism. It is also interesting that Job, who suffered from persistent itching and weeping dermatitis, seems to have been cured, finally, merely by adhering to a salt-free diet (The Book of Job, chapter 6, verses 6 and 7). The earliest account of the etiology, symptoms, and treatment of vitamin deficiency appeared about A.D. 392, when St. Jerome described a skin disease suffered by St. Hilarion as the result of four years of diet limited to barley bread and vegetables cooked without oil. It appears that addition of oil to the diet was followed by recovery (Taylor[1]). There is nothing new under the sun. Twenty-five hundred years before Gerson's time, an unknown, obscure physician prescribed a salt-free diet for a patient with dermatitis, and fifteen hundred years ago the clinical picture of vitamin A deficiency was described.

For centuries, dietary therapy has played a more or less prominent role in the management of skin diseases. The relative stress laid on this approach was largely dependent, of course, on the dominant views of the medical profession at a given period. From the very dawn of history, folk medicine, nature healers, and the like have been inclined to blame foods for causing skin diseases in human beings and animals. Throughout the ages writers and poets of many lands have mentioned the efficacy of dietary and mineral water cures in the treatment of dermatoses. Moreover, it has long been known among animal breeders and farmers in general that faulty nutrition will exert an unfavorable influence on the texture of an animal's skin and on the fineness and gloss of its coat.

The physicians of the seventeenth and eighteenth centuries attempted, in accordance with the humoral-pathologic views of that period, to interpret every skin disease as the expression of an improper mixture of the humors. They therefore regarded every skin lesion as a manifestation of an underlying dyscrasia, to be treated along dietary lines. The very drastic measures which were then commonly employed and which included excessively prolonged thirst and hunger cures naturally, since they were often unsuccessful, caused the pendulum to swing too far in the other direction and served to discredit the dietary therapy of cutaneous disorders. In fact, under the influence of the teaching of cellular pathology the most distinguished members of the school of German dermatology (Hebra, Kaposi, Unna, J. Jadassohn, Bloch) categorically rejected the very idea that diet might be an etiologic factor in the causation of skin diseases.

On the other hand, ever since the latter part of the nineteenth century the French, under the leadership of Brocq,[2] have stressed the importance of the *régime alimentaire* in dermatoses. They have regarded faulty digestion and assimilation of food as the paramount factor in the causation of many skin eruptions and associated symptoms. In America G. H. Fox,[3]

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1. Taylor, F. S.: Nature 154: 802, 1944.
2. Brocq, L.: Traite elementaire de dermatologie pratique. Paris: Doni, 1907.
3. Fox, G. H.: J. Cut. Dis. 25: 152, 1907.

Stelwagon,[4] and Bulkley[5] were the leaders of the school of thought which believed in decreasing the intake of food in order to counteract the effects of overnourishment; this approach, as well as the institution of a strictly vegetarian diet, they believed, might exert a marked influence on a number of skin conditions.

Last, we find a middle-of-the-road group in every country, moderates who take the stand that an appropriate diet may indeed give appreciable support to local therapeutic measures, but who insist that complete success can never be achieved by dietary procedures alone.

Luithlen's[6–9] experimental studies of the chemistry of the skin stand as a milestone in the history of dietary therapy in cutaneous diseases. The most ardent supporters of nutritional therapy had previously been unable to submit anything more than general indications that there must be a connection between certain foods and certain skin conditions, having failed to prove their point because they lacked the proper procedure. But, as will be discussed in some detail in Chapter I, Luithlen demonstrated in his animal experiments that various forms of diet can exert a strong influence on the skin's irritability and reactivity. He further showed that certan changes in the chemical composition of the skin make their appearance at the same time. Thus, Luithlen was the first to reveal the highly significant fact that there is a definite connection between the nature of the diet on the one hand and the skin's chemistry and irritability on the other.

Moreover, not only the mineral content of the skin, but also its water,[10] carbohydrate,[11] and nitrogen[12] metabolism is definitely subject to dietary influences. For many years the present writer has pointed to the fact that, in the study of the physiology and pathology of the skin, a chemical analysis of tissue excised from the living organism gives a far better insight into the metabolic process of the organ than does a study of the blood alone. He[13] introduced the electric punch-biopsy method, by which skin specimens can be removed almost painlessly, without need of anesthesia, even when the procedure is performed repeatedly for a series of studies. At the same time microchemical methods were developed[11, 14] which made it possible to carry out accurate quantitative chemical determinations on minute particles of tissue.

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4. Stelwagon, H. W.: J. Cut. Dis. **25:** 147, 1907.
5. Bulkley, L. D.: Diet and Hygiene in Diseases of the Skin. New York: Hoeber, 1913.
6. Luithlen, F.: Wien. Klin. Wchnschr. **24:** 703, 1911.
7. Luithlen, F.: Wien. Klin. Wchnschr. **25:** 658, 1912.
8. Luithlen, F.: Arch. f. exper. Path. u. Pharmakol. **68:** 209, 1912.
9. Luithlen, F.: Zentralbl. f. Haut- u. Geschlechtskr. **7:** 1, 1923.
10. Urbach, E.: Arch. f. Dermat. u. Syph. **156:** 73, 1928.
11. Urbach, E. and Lentz, J. W.: Arch. Dermat. & Syph. **52:** 301, 1945.
12. Urbach, E. and Sicher, G.: Ztschr. f. d. ges. exper. Med. **76:** 483, 1931.
13. Urbach, E. and Fantl, P.: Biochem. Ztschr. **196:** 471, 1928.
14. Urbach, E. and Fantl, P.: Wien. Klin. Wchnschr. **38:** 384, 1925.

The question of nutritional therapy in skin diseases was again placed in the spotlight when Gerson,[15] alone at first, and then in collaboration with Sauerbruch and Herrmannsdorfer,[16] demonstrated that a low salt diet brought excellent results in certain forms of skin tuberculosis. This dietary was soon tried in other acute and chronic inflammatory conditions of the skin, sometimes with very good results.

But it was the discovery of vitamins and the demonstration of their clinical efficacy that really brought nutritional therapy into its own in certain skin diseases. It can by no means be said that investigation in this field has been completed. However, the concerted efforts of biochemists, experimental investigators, and clinicians have already produced impressive therapeutic results. Diseases such as pellagra, phrynoderma, keratosis follicularis, pityriasis rubra pilaris, cheilosis, tropical ulcer, and others, which were regarded as hopeless, or at least intractable, only ten years ago, can now be cured in a few months.

Furthermore, we are just beginning to have an understanding of that type of deficiency which has come to be called subclinical. This is now recognized as being equal in importance to any frank deficiency disorder. However, better and simpler technical procedures, suitable for clinical use, are needed to facilitate the recognition of nutritive deficiencies. The introduction of appropriate bio-assays and microchemical methods will surely make it possible in the near future to recognize borderline cases. This will help to reveal the origin of a number of other dermatoses, including notably those in which changes of the epithelium and of the appendages of the skin (hair, nails), as well as of the capillaries, are histologically demonstrable.

Countless animal experiments have been performed to determine the influence of vitamin deficiencies on the gross and microscopic pathology of the skin. These experiments have had to be carried out on animals because only in this way has it been possible to isolate each individual nutritional factor and thus obtain reasonably reliable experimental conditions. While such investigations are unquestionably valuable, they all suffer from one incontestable weakness. Because different animal species may respond variously, direct conclusions as to the clinical application of a given nutritive agent in human beings cannot possibly be drawn. The true value of each factor can be determined only by clinical observation or by direct experimentation in human beings. Moreover, we should not overlook the point that in cases of malnutrition we are rarely confronted with just a single vitamin deficiency.

Skin diseases may be caused not only by malnutrition due to vitamin deficiencies, but also by malnutrition resulting from a lack of proteins

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15. Gerson, M.: Diättherapie der Lungentuberkulose. Vienna: Deuticke, 1934.

16. Sauerbruch, F. and Herrmannsdorfer, A.: München med. Wchnschr. 75: 35, 1928.

or from a diet consisting mainly of inferior vegetable proteins, as is now regrettably the case in the famine-stricken areas of India and China. Recent investigations have also shown that insufficiency of an essential amino acid may cause specific changes in the human body; and it is to be noted that fatty acid deficiency may cause disease (Burr and Burr[17]).

The effects of nutritional anomalies in the production of dermatoses are closely linked with the metabolism and the biochemistry of the skin. There can be no doubt that current investigations along such chemical lines will presently result in a number of highly significant discoveries. As Elvehjem,[18] the distinguished pioneer in nutritional biochemistry, recently pointed out, we are today only beginning to realize the interrelationship of all nutrients and the interdependence of one factor with another. For instance, we know that during the release of energy from carbohydrate in the body, phosphoric acid, co-enzymes containing vitamins, enzymes containing iron, and other enzymes activated by magnesium and manganese are all needed to complete the process. The lack of one or another constituent in the diet may explain the inadequacy in certain enzyme systems which is demonstrable in severe nutritional deficiencies. On the other hand, the inactivation by chronic metallic poisoning—e.g., by zinc chloride—of an enzyme which is partly formed of vitamins may create a demand for an excessive amount of those vitamins. As Gross[19] has shown, this causes a vitamin deficiency which leads to skin manifestations identical with those known to result from experimental pantothenic acid deficiency. The importance of the lack of antioxidants in experimental diets is now the subject of interesting investigations regarding the mechanism for producing vitamin deficiencies (Sullivan and Evans[20]). It must be emphasized that inadequacy of an aliment in a diet and disease of the gastro-intestinal tract preventing proper absorption are not the only means by which deficiency results. The demonstration of avidin-biotin conditioning, for example, has revised the narrow concept of excluding the probability of deficiency disease because of a history of an adequate diet (György et al.[21]).

Important progress has also been made in the discovery of the mode of action of the so-called "trace elements,"* indicating that the role of traces is one of participation in the activities of enzymes and hormones, a role in all probability analogous to that of the vitamins (Shils and McCollum[22]). Thus, a diet extremely low in zinc produced a hyperkeratinization of the skin, thickening of epidermis, and loss of hair follicles with persistence of the sebaceous glands as revealed in microscopic study (Follis and Day[23]).

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* Trace element is the name given to any element occurring in the tissue in amounts equal to or less than iron. To date at least 23 trace elements have been reported. Of principal nutritional interest are iron, copper, iodine, manganese, cobalt, zinc, fluorine, selenium, boron, and aluminum (Shils and McCollum[22]).

17. Burr, G. O. and Burr, M. M.: J. Biol. Chem. **82:** 345, 1929.
18. Elvehjem, C. A.: Med. Clin. North America **27:** 277, 1943.
19. Gross, P., Harvalik, Z., and Runne, E.: J. Invest. Dermat. **4:** 385, 1941.
20. Sullivan, M. and Evans, V. J.: Arch. Dermat. & Syph. **49:** 33, 1944.
21. György, P., Rose, C. S., Eakin, R. E., Snell, E. E., and Williams, R. J.: Science **93:** 477, 1941.
22. Shils, M. E. and McCollum, E. V.: J. A. M. A. **120:** 609, 1942.

Finally, the fundamental studies of Schoenheimer[24] and his associates with "isotopically" marked compounds must be mentioned. By using the heavy isotopes* of hydrogen, carbon, and nitrogen as well as the radioactive isotope of sulfur as markers of particular amino acids or fatty acids, Schoenheimer has shaken the classic theory of the more or less static state of body protein—i.e., that the protein synthesis in the adult animal is restricted largely to replacing losses due to the wear and tear of metabolism. In experiments with orally administered "tagged" amino acids or fatty acids he has shown that they are rapidly and extensively incorporated as such in tissue protein and in the fat tissue of the various organs. These investigations explain clearly the marked influence of dietary constituents on the composition of the tissues, including the skin. This is very pointedly exemplified by the fact that hogs in the South receiving high proportions of cottonseed oil in their fodder form a "soft" pork while hogs in the Middle West on a corn diet form a "hard" pork.

Dietary therapy plays a distinguished role in another group of skin diseases—namely, those cases of urticaria, angioneurotic edema, lichen urticatus, dermatitis (eczema), neurodermatitis, and infantile dermatitis which are due to food allergy. The problem of identifying the responsible food allergen in a given case was greatly facilitated when Rowe[25] introduced his "elimination diets." The same purpose is served by the present writer's[26] "Propeptan test diet," with which the responsible food allergen or allergens can be identified in a short time without drastic changes in the patient's diet. Once the identity of the food antigen or antigens has been established, deallergization with the corresponding Food Propeptan is a rather simple matter.[26]

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* Isotopes are chemical elements which differ from those commonly found in nature only in their mass or atomic weight or their radioactivity. This makes it possible to determine accurately microquantities of these isotopes in any tissue. It is thus apparent that by incorporating one or more isotopes into a given substance the latter is labeled or tagged so that it can be followed in the organism and its concentration in the substance or tissue which contains it can be determined.

23. Follis, R. H., Jr., Day, H. G., and McCollum, E. V.: J. Nutrition 22: 223, 1941.
24. Schoenheimer, R.: The Dynamic State of Body Constituents. Cambridge, Mass.: Harvard University Press, 1942.
25. Rowe, A. H.: Food Allergy. Philadelphia: Lea and Febiger, 1931.
26. Urbach, E. with the collaboration of Gottlieb, P. M.: Allergy. New York: Grune and Stratton, 1943.

Furthermore, it is becoming more and more apparent that some skin diseases are merely the cutaneous expression of a more general disturbance caused by diseases or dysfunction of the gastrointestinal tract, the liver, pancreas, kidneys, the vascular or nervous system, or the endocrine glands. As for the extent to which such secondary cutaneous manifestations can be controlled by dietary measures aimed at influencing the primary disease in the affected internal organ, this question will be discussed in some detail. Metabolic diseases will be considered in so far as they have a direct bearing on the relationship between nutrition and skin diseases. We realize, however, that the metabolic and the cutaneous changes may at times be related not as cause and effect but as concomitant manifestations, both being due to the same underlying etiologic factors. Lastly, changes in the internal organs and in metabolism, as well as other aberrations accompanying skin affections, may be the result rather than the cause of the cutaneous disorder. Thus we know that transient disturbances of the carbohydrate metabolism can be caused by extensive inflammatory skin conditions as well as by cutaneous infections. This would seem to demonstrate that a metabolic anomaly may basically be of peripheral origin.

Let us now consider some of the fundamental principles of nutritional therapy proper.

We can prevent ourselves from falling victims to dietetic fads if we will keep the following basic requirements of nutrition in mind: (1) the maintenance of nitrogenous equilibrium; (2) energy-bearing food sufficient to maintain the caloric equilibrium under the individual's conditions of life; (3) certain fresh or raw foods; (4) a certain percentage of vegetable fiber; (5) various salts needed by the body; (6) certain materials that add savor to the food and stimulate the secretion of gastric juice; (7) reasonable demands of taste and bulk.

A diet which fails to meet these requirements is not to be prescribed for more than a short time. When it is prescribed it must always be borne in mind that the patient is receiving an unbalanced diet, which, if continued for any length of time, will inevitably lead to some manifestation of malnutrition.

In addition to the curative factors directly dependent upon the somatic action of a diet, there are certain psychological imponderables which must never be overlooked. The physician should always remember when he sets out to prescribe a diet that savoriness, variety, and an appetizing appearance are very important gastronomically. Furthermore, the physician must be able to exert a considerable amount of personal influence, particularly in cases demanding a salt-free diet, for example, which puts quite a strain on the patient's will power.

The persistence of an inflammatory condition of the skin may often depend not only on what the patient eats, but also on how, when, and under what circumstances he eats. Hasty eating, irregular eating (with regard both to the principal meals and to in-between snacks), and also meals taken under the stress of excitement or worry will adversely influence the patient's autonomic nervous sytem and thus also the nutrition of the skin. Inadequate mastication, often due to missing teeth, and insufficient insalivation are other points about which the patient should be educated. Furthermore, the question of evacuating the bowels regularly is of prime importance in many diseases of the skin. Adequate rest, of the right kind, and regularity in the hours of sleep are also essential factors.

Finally, it is impossible to overemphasize the fact that most of us eat too much. Many individuals continue to gratify the sense of taste long after the appetite is satisfied.

To be really proficient in the field of dietary therapy, one must have not only a thorough understanding of the nutrition of the healthy and of the sick, but also practical training in the preparation of food, a subject which neither the medical student nor the intern will find on his curriculum. However, some children's clinics have recently initiated practical courses in cooking, which physicians and nurses alike are obliged to attend. We feel that practical experience in the diet kitchen and theoretical training in the science of nutrition should be a requisite in medical education.

PART ONE

THE INFLUENCE OF NUTRITION ON THE PHYSIOLOGY OF THE SKIN

CHAPTER I

Metabolism and Biochemistry of the Skin

CLINICAL observations have long suggested that the diet has some influence on the chemical composition of the skin, and thus on cutaneous susceptibility to disease. But it required modern, experimental dermatology, with its precise methods of chemical investigation, to bring the long-awaited conclusive proof of what the older dermatologists had only intuitively surmised on the basis of their clinical observations.

The connection between diet and cutaneous diseases is not to be interpreted as meaning that variations in the chemical composition of the diet are, in themselves, the cause of skin manifestations. This had been pointed out by Luithlen, who may be regarded as the founder of investigative dermatology along chemical lines. He explained that changes in the diet so influence the skin that it will offer decreased or increased resistance to various external stimuli and internal influences, depending on the type of diet.

In the following paragraphs we shall show that the water, mineral, carbohydrate, lipid, and nitrogen metabolism of the skin is directly dependent upon the nature of the diet. For years, the present writer[27, 28] has stressed the point that this question cannot be accurately studied by carrying out chemical analyses of the blood alone, but that it is of fundamental importance to examine biopsy specimens of the living skin chemically. Generally speaking, the blood consistently maintains the concentrations of its varicus chemical constituents within very narrow limits. On the other hand, the concentrations of these same chemical constituents in the tissues may vary widely, both with metabolic and with disease processes. Therefore there is no dependable equilibrium between the respective inorganic and organic components of the blood on the one hand and the tissues on the other. This will be demonstrated by a number of examples. Rosenberg[29] carried out a series of precise nitrogen balance studies showing that patients with renal disturbances retain far more nitrogen than the increase in the nonprotein nitrogen in the blood would indicate; and that, on the other hand, patients recovering from uremia eliminate far greater quantities of nitrogen than would be expected from

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[27] URBACH, E.: München. med. Wchnschr. **78:** 89, 1931.

[28] URBACH, E.: Wien. klin. Wchnschr. **41:** 581 and 634, 1928.

[29] ROSENBERG, M.: Deutsche med. Wchnschr. **47:** 1488, 1921.

the decline in the nonprotein nitrogen of the blood. In this connection, it is interesting to note Nonnenbruch's[30] report that in patients with edema he not only found no hydremia in many cases, but sometimes actually observed increased blood concentration. Similarly, Thannhauser[31] showed that in nephritis there is a sharp rise in the sodium chloride content of the edema fluid after administration of large quantities of table salt, while the sodium chloride concentration and the water content of the blood serum remain virtually unchanged. In pemphigus the present writer[32] has repeatedly found the chlorine level in the blood to be normal, while it was abnormally high in the skin. In burns the author has noted a decline in the chlorine levels in the blood and urine, accompanied by a rise in the chlorine content of the skin. Knudson[33] et al. observed a great increase in the total cholesterol of the skin in rats subjected to irradiation with ultraviolet light until skin tumors appeared, while at the same time the cholesterol in the blood fell to subnormal levels. The unreliability of chemical blood studies as an index of skin chemistry is further shown by the fact that hypercholesterodermia is by no means necessarily accompanied by hypercholesterinemia—not even in cases of very widespread xanthomatosis (Siemens[34]). Other examples are hyperuricodermia without hyperuricemia (Gudzent[35]) and hyperglycodermia without hyperglycemia (Urbach[36]). In this connection we may recall that some cases of leukemia of the skin present an apparently normal cytologic blood picture.

Chemical analyses of the tissues proper cannot by any means be replaced by studies of cantharides-blister fluid, as used by Gaensslen,[37] Wohlgemuth and Scherk,[38] and others. For, as the writer[39] has shown, contents of the blisters are chemically almost identical with the blood serum and grossly different from the skin as determined by direct analysis of the tissue itself. Therefore, the claim of Gaensslen that blister fluid represents tissue fluid is unfounded.

Table 1 shows that the blood serum and the skin present totally different values for most of the chemical components. Therefore, determinations of the sugar, chlorine, and nonprotein nitrogen levels of the blood, for example, give no information as to the values of these substances in the skin.

30. Nonnenbruch: Deutsche Arch. f. klin. Med. **136:** 170, 1921.
31. Thannhauser, S. J.: Ztschr. f. klin. Med. **89:** 181, 1920.
32. Urbach, E.: Arch. f. Dermat. u. Syph. **150:** 52, 1926.
33. Knudson, A., Sturges, S., and Bryan, W. R.: J. Biol. Chem. **128:** 721, 1939.
34. Siemens, H. W.: Arch. f. Dermat. u. Syph. **138:** 431, 1922.
35. Gudzent, Wille, and Keeser: Ztschr. f. klin. Med. **90:** 147, 1920.
36. Urbach, E.: J. A. M. A. **129:** 438, 1945.
37. Gaensslen, M.: München. med. Wchsnchr. **69:** 1176, 1922; **70:** 1015, 1923; **71:** 198, 1924.
38. Wohlgemuth, J. and Scherk, G.: Klin. Wchsnchr. **8:** 1363, 1929.
39. Urbach, E.: Klin. Wchnschr. **8:** 2094, 1929.

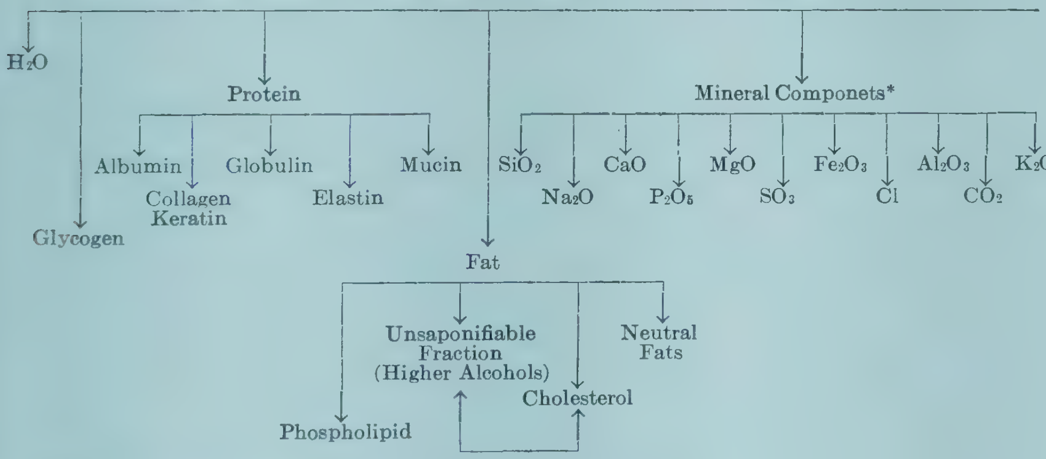
For the purpose of excising small quantities of skin speedily and with little discomfort, the present writer[11, 13] has perfected a practical and simple method of taking biopsy specimens. This technic provides reasonably uniform material, and thus makes possible the carrying out of systematic microchemical studies of the human and animal skin, under physiologic and pathologic conditions. The method consists of using a rotating punch, similar to a dentist's drill, which removes cylindrical pieces of skin

TABLE 1.—*Comparison between Some of the More Important Constituents of Blood and Skin*

Constituent	Normal Value in Mg. Per Cent	
	Blood Serum	Fresh Skin
Water	910	610–675
Total nitrogen*	960–1280	3500–4000
Nonprotein nitrogen	20–40	70–80
Amino acid nitrogen	4–4.5	17–38
Sugar	80–120	55–68
Total cholesterol	160–250	250±
Cholesterol esters	110–170	160±
Chlorides, calculated as sodium chloride	560–600	200–320
Sodium	300–330	95–139
Potassium	18–23	60–119
Calcium	9–12	9–15
Magnesium	1–3	7–12

* Since protein contains about 16 per cent nitrogen, it is conventional to convert percentage of nitrogen to percentage of protein by multiplying by 6.25.

TABLE 2.—*Chemical Composition of the Skin* (McLaughlin and Theis[40])


H_2O
Protein
Mineral Componets*
Albumin
Globulin
Mucin
Collagen
Keratin
Elastin
Glycogen
SiO_2
Na_2O
CaO
P_2O_5
MgO
SO_3
Fe_2O_3
Cl
Al_2O_3
CO_2
K_2O
Fat
Unsaponifiable Fraction (Higher Alcohols)
Neutral Fats
Cholesterol
Phospholipid

* Probably combined as Na_2SiO_3, $Ca_3(PO_4)_2$, $Mg_3(PO_4)_2$, NaCl, KCl.

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[40] McLaughlin, G. D. and Theis, E. R.: J. Am. Leather Chem. Assoc. 19: 428, 1924.

that are always of the same size, being 5 mm. in diameter and weighing about 150 mg. These are snipped off from their base in the subcutaneous tissue with scissors. The procedure is almost painless and does not call for anesthesia of any kind. Furthermore, the writer has developed microchemical methods which permit accurate determination of sugar, chlorides, protein and its degradation products in minute tissue particles.

In the present chapter we shall endeavor to show that investigations of the chemistry of the skin *in vivo* are not only of great help in the study of nutritional problems of the skin, both from the physiologic and the pathologic point of view, but also offer countless possibilities for future research. For a better understanding of these relationships it is necessary to summarize our present knowledge of the chemistry of the skin and to examine critically the influence of diet on the skin's chemistry. Table 2 gives a graphic presentation of the more important organic and inorganic constituents of the skin.

For more detailed information on the chemistry of the skin, the reader is referred to the excellent and comprehensive monographs and papers by Rothman and Schaaf,[41] Perutz,[42] Markowitz,[43] and Cornbleet,[44] as well as to a review by the present writer.[45]

A. WATER METABOLISM OF THE SKIN

The water content of the living skin obtained by the electric punch method varies within relatively narrow limits (61 to 67.5 per cent) and is considerably lower than the water content of all the other organs of the body (70.8 to 78.9 per cent), with the exception of bone and fatty tissue. The above figures, which were first established by the present writer,[10] apply only to adults' skin freed of subcutaneous tissue. In this connection it is interesting to note that the upper and denser part of the cutis, the stratum papillare, contains roughly 10 per cent more water than does the lower, more loosely arranged layer, the stratum reticulare. In animals the skin is likewise relatively poor in water (average figures: rat, 60 per cent; bull, 61 per cent; calf, 63 per cent; dog, 64 per cent; guinea pig, 70 per cent; rabbit, 71 per cent). In man the underlying pathologic processes seem to determine the layer of skin in which most of the water retention takes place. Generally speaking, however, the stratum reticulare, if only because of its considerably greater volume, would appear to possess the greater storage capacity.

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41. Rothman, S. and Schaaf, F.: Chemie der Haut. in Handb. d. Haut- u. Geschlechtskr. Berlin: Springer, 1929.
42. Perutz, A.: Die Pharmakologie der Haut in Handb. d. Haut- u. Geschlechtskr. Berlin: Springer, 1930.
43. Markowitz, M.: Practical Survey of Chemistry and Metabolism of the Skin. Philadelphia: Blakiston, 1942.
44. Cornbleet, T.: Urol. & Cutan. Rev. **45:** 451, 1941.
45. Urbach, E.: Zentralbl. f. Haut- u. Geschlechtskr. **26:** 217, 1928.

Because it will frequently be necessary to refer to the subcutaneous tissue, it is desirable to stress the wide variations which occur particularly in the water and fat content in this tissue. As Lasch[46] has shown, the water content of the subcutaneous tissue is especially high in nurslings. However, it varies to some extent according to the region of the body from which the specimen is obtained, this being true for persons of all ages. With regard to the influence of nutrition, it is well known that the subcutaneous tissues' water content is definitely dependent on the nutritional state of the individual. More than one hundred years ago, Chossat noted that during starvation the water content of the subcutaneous tissue as well as of other organs increased notably. Bozenraad[47] and Schirmer[48] established this fact quantitatively by demonstrating that the subcutaneous tissue of obese persons contains less water than that of thin subjects. Thus, while it has a water content of between 5 and 13 per cent in the former, that in an emaciated patient may be as high as 70 per cent. These differences are explained by the fact that the subcutaneous tissue of obese persons contains more fat and less connective tissue, and the latter alone can hold tissue water.

In the skin, as in every organ, the water level is largely dependent upon three factors: age, state of nourishment, and the possible presence of disease in the individual. Furthermore, the cutaneous water content varies with the region of the body in a manner similar to that of the subcutaneous tissue (Nadel[49]). In view of this fact, the present writer has suggested that all studies be made on skin taken from the upper lateral aspect of the thigh.

The skin of infants and small children is normally extraordinarily rich in water (and so, indeed, is the entire organism of infants). Thus, a healthy infant's skin contains 81 to 82 per cent water, and in pathologic cases the figure may go as high as 92 per cent (Klose[50]). As the child grows older, the organs normally contain less and less water. However, as found by the present writer,[10] the water content of the senile, atrophic, parchmentlike skin of the aged again reaches relatively high levels (72 to 74 per cent). This observation has been confirmed by Buerger and Schlomka[51] and Herrmann.[52] This does not, however, represent actual water retention, as in edema, for an incision into such senile skin will show the tissues to be quite dry. The explanation of the high cutaneous water content may

[46] Lasch, W.: Jahrb. f. Kinderh. **107:** 223, 1924.

[47] Bozenraad, O.: Deutsche Arch. f. klin. Med. **103:** 120, 1911.

[48] Schirmer, O.: Arch. f. exper. Path. u. Pharmakol. **89:** 263, 1921.

[49] Nadel, A.: Arch. f. Dermat. u. Syph. **165:** 507, 1932.

[50] Klose, E.: Jahrb. f. Kinderh. **80:** 154, 1914; **91:** 157, 1920.

[51] Buerger, M. and Schlomka, E.: Ztschr. f. d. ges. exper. Med. **63:** 105, 1928.

[52] Herrmann, F.: Ztschr. f. d. ges. exper. Med. **76:** 780, 1931.

be that the changes in the physical and chemical character of the elastic and collagenic fibers of the cutis incident to old age result in a physicochemical disturbance of the tissue colloids and thus lead to an increased tendency to store water.

This raises the question as to how water is held in the skin of healthy individuals as well as under pathologic conditions. Normally water is stored in the colloid tissue of the cutis in the form of "swelling water."* The swelling water of the tissues is constantly increasing or decreasing in quantity, depending on physicochemical processes. On the basis of Fischer's[53] fundamental experiments, it seems probable that when these physicochemical influences become pathologic they may cause abnormal cutaneous water retention. Instances of such disturbances are presented by the pre-edematous state of the skin as, for example, in early nephrosis or by the high water content of the skin in exudative diathesis of young children.

As demonstrated by Fischer,[53] the close analogy between the water-absorbing power of certain protein colloids *in vitro* and that of the tissues would seem to warrant the conclusion that the physicochemical status of the protein colloids chiefly, if not wholly, determines the relative amounts of water in a given tissue under various circumstances. Thus the question of the capacity of the tissues to store water becomes a matter of colloid chemistry, which explains why the problem must be studied with the aid of colloidal-chemical methods. Since this highly important field of investigation cannot be discussed in detail here, the reader is referred to the monographs and papers of Schade,[54] Schade and Menschel,[55] Memmesheimer,[56] Herrmann,[52, 52a] and Stern.[57] In brief, pre-edema in general represents a pathologic increase in the physiologic water storage process. While the increase in water has up to the present time been determined only by means of continuous determination of the body weight, with all the errors inherent in this method, our punch-biopsy method makes it possible to perform accurate quantitative chemical determinations in the living skin. However, the great obstacle to further investigation in this direction lies mainly in the fact that we are unable to bring about experimental changes in the water-absorbing capacity of the tissue colloids of the living organism.

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* The term "swelling wate:" (or "*Quellungs wasser*") denotes the water which is loosely incorporated in the intracellular tissue colloids, in contrast with the extracellular water stored in the interstitial spaces of the tissue, as in edema.

52a. Herrmann, F.: Dermat. Ztschr. **50:** 277, 1927.
53. Fischer, M. H.: Kolloidchemie der Wasserbindung. Steinkopf, 1927.
54. Schade, H.: Jahresk. f. ärtztl. Fortbild. **14:** 10, 1923.
55. Schade, H. and Menschel, H.: Ztschr. f. klin. Med. **96:** 279, 1923.
56. Memmesheimer, A. M.: Arch. f. Dermat. u. Syph. **152:** 385, 1926.
57. Stern, F.: Arch. f. Dermat. u. Syph. **164:** 573, 1932.

The fact that the diet exerts a profound influence on the water content of the body, and notably that the organs of animals raised largely or exclusively on carbohydrates contain more water than do those of animals on a low carbohydrate diet, has already been demonstrated by Bischoff and Voit.[58] On an inadequate diet the water content of the skin commonly increases, as a result of a decrease in fat. However, variations in the amounts of fat and of water in the skin proper are not always in inverse relationship. It has been demonstrated, notably by Steinitz and Weigert,[59] that fluctuations in the amount of water are dependent not only on changes in quantity of the fat in the tissues, but on their content of nitrogenous substances and salts, which is largely determined by the diet as well as by pathologic processes.

Sakata[60] demonstrated that the water content of the skin of rabbits is directly dependent upon the nature of the diet (moist or dry fodder). While the skin of animals receiving adequate quantities of water shows an average water content of 72 per cent, the water level was found to be as low as 62.7 per cent in the skin of animals which had been deprived of water for eight days; in these same animals, the other organs had lost negligible amounts of water. Koenigstein,[61] who performed similar experiments on guinea pigs, observed that, after seven days without food or water, the average loss of water was 9 per cent in the skin and only 1.7 per cent in the muscle tissue.

The significance of the skin as a water depot is more readily apparent in infancy and early childhood than in adult life. Thus, in the majority of infants who die of some acute nutritional disturbance, there is a marked decline in the skin water content (a drop from the normal level of 82 per cent to 70.7 per cent, Klose[50]). On the other hand, considerable increases in the water content of the skin were observed by Tobler and Bessau[62] in cases of alimentary water retention due to a disproportionate carbohydrate diet, and by Klose[50] in infants with chronic alimentary disturbances.

This conforms perfectly with Lederer's[63] experimental studies on animals, in which it was found that the beginning of physiologic dehydration is delayed in animals exclusively breast-fed beyond the normal weaning time; and similarly, that the dehydration which normally occurs as the organism grows older is also delayed in dogs fed exclusively on a diet of cow's milk, after the normal weaning date. Lederer believes, furthermore, that physiologic dehydration is also delayed in children with exudative

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58. Bischoff, T. L. and Voit, C.: Die Gesetze der Ernährung des Fleischfressers. Leipzig, 1860.
59. Steinitz, F. and Weigert, R.: Jahrb. f. Kinderh. **61:** 146, 1905.
60. Sakata, S.: Arch. f. exper. Path. u. Pharmakol. **105:** 11, 1925.
61. Koenigstein, H.: Arch. f. Dermat. u. Syph. **154:** 352, 1928.
62. Tobler, L. and Bessau, G.: Allg. path. Physiologie d. Ernährung u. d. Stoffwechsels im Kindesalter. Wiesbaden, 1914.
63. Lederer, R.: Ztschr. f. Kinderh. **10:** 365, 1914.

diathesis, either by prolonging the nursing period or by drinking cow's milk too long or too freely, or by eating a malproportioned diet of bread and potatoes, or lastly by drinking too much water.

Of practical interest is Schiff's[64] emphasis on the fact that when the water intake is restricted and high protein food (milk) is given, cutaneous turgescence decreases considerably so that the raised skin remains elevated in folds. These clinical manifestations fail to appear when protein-free food is given in connection with similar water restriction. This shows to what extent the water requirements are dependent upon the quantity of protein in the diet.

The balance between the various ions also exerts considerable influence on the water metabolism. The investigations of Freudenberg and György,[65] Oehme,[66] and others have disclosed the fact that acidosis leads to a decrease of swelling water in the tissues with consequent diuresis, while alkalosis, on the other hand, causes an increase in swelling water.

Lastly, mention must be made of Veil's studies,[67] which show that water itself is an effective diuretic agent, since it opens up the salt depots in the skin. Hashimoto, confirming Ginsberg's findings, reported that tap water is a diuretic and that distilled water is not, but more recent experiments (Glaessner[68]) would seem to show that distilled water, consistently taken in great quantities (2 liters), also serves to flush out the salt depots.

All of these observations lead to the conclusion that the skin is the only organ to possess an appreciable water reserve which can be shunted about within the organism as needed by other tissues, and notably by the blood to maintain its constant water level. Although the other organs contain more water than does the skin, their water content is reserved almost exclusively for their own requirements and must therefore be considered as bound "fast" and not "loosely" in these tissues. According to Schade,[54] the connective tissue of the skin is admirably suited to this role because of its great masses of extracellular colloid, consisting of homogenous as well as collagenous and elastic fibers, which make for spaciousness and extensibility.

The water content of the skin is largely dependent upon existing pathologic conditions, including diseases both of a general nature and those involving cutaneous disturbances. As for the former category, we have already given some data concerning the rise and fall of the water level in the skin of infants. In adults, cases of clinically demonstrable cutaneous edema (due, for example, to cardiac decompensation or to renal insufficiency) show increases in the cutaneous water content to levels as

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64. Schiff, E.: Das Exsiccoseproblem. Berlin: Springer, 1929.
65. Freudenberg, E. and György, P.: Biochem. Ztschr. **124:** 299, 1921.
66. Oehme, C.: Ergebn. d. inn. Med. u. Kinderh. **30:** 1, 1926.
67. Veil, W. H.: Ergebn. d. inn. Med. u. Kinderh. **23:** 648, 1923.
68. Glaessner, K.: Wien. med. Wchnschr. **80:** 623, 1930.

high as 73 per cent in the cutis and 66 per cent in the subcutaneous tissue. The difference between acute inflammatory dermatoses and an edematous, waterlogged skin (as in congestive heart failure) lies not so much in the water level as in the salt content. This is because the chlorine levels in the latter condition are so high, as a result of absorption of sodium chloride by the waterlogged tissues from the blood, that the chlorine level of the blood itself is very nearly attained.

Koenigstein's[61] experimental studies have demonstrated that certain endocrine organs are capable of exerting a profound influence on the water metabolism of the skin. While the water content of the skin of guinea pigs is normally 65 per cent, Koenigstein found that removal of the thyroid and parathyroids was followed in a considerable number of cases by a decline in the water content of the cutis to a level of 52 per cent. However, this operation apparently has no effect on the water content of the blood, internal organs, and muscle tissues. Later investigations by Koenigstein[61] indicate that the water metabolism of the skin seems to be normally regulated chiefly by the parathyroids and not, as previously believed, by the thyroid gland. It has been observed in dogs that the removal of the thyroid alone brought about a slight decline in the cutaneous water content, while removal of the parathyroids alone was followed by a very sharp decline in the water level in the skin. Here, too, the other organs showed no appreciable changes with regard to their water content. As is well known, thyroid gland preparations are most helpful in combating excessive water in the skin, as seen in myxedema and in many forms of adiposity.

The present writer[10] has studied the water content of the skin in a number of dermatoses (Table 3).

TABLE 3.—*Percentage of Water in Normal and in Pathologic Skin*

	Cutis	Subcutaneous Tissue
Normal adult	61–67	11–20
Dermatitis, acute	80.3	61.9
Erythroderma	75.2	
Erysipelas	76.1	51.9
Psoriasis, subacute	77.4	55.2
Ichthyosis	71.7	16.1
Scleroderma	71.3	33.1
Dermatitis atrophicans, atrophic stage	80.2	43.1
inflammatory stage	77.9	31.7
Obesity	70–72	11–26
Acromegaly	67.1	49.2
Diabetes insipidus	62.9	

In acute inflammatory dermatoses, including dermatitis, erythrodermia, erysipelas, and acute psoriasis, we naturally expect to find abnormally high water levels in the cutis and subcutaneous tissue of the affected skin. In such dermatoses Ackermann was able to demonstrate a subnormal renal output directly proportionate to the extent of the pathologic cutaneous process, together with normal concentrating power in the kidneys. The finding that the seemingly dry skin of ichthyosis, the hard skin of scleroderma, and the atrophic skin of dermatitis atrophicans is very rich in water is worthy of special note; as in the atrophic skin of old age, this high water level may well be due to a biochemical disturbance of the cutaneous colloids in regard to their capacity to store water.

In conformity with the clinical appearance, the toes in acromegaly show increased quantities of water in the cutis and especially in the subcutaneous tissue. The low water and sodium chloride levels, which we found in the skin of a patient with diabetes insipidus, correspond perfectly with our hypothetical expectations; for it has long been assumed that this disease involves a pathologic shift of water from the tissues to the blood.

The widespread clinical assumption that the skin's water content is abnormally high in obesity induced us to examine the question more closely from the chemical viewpoint. Although Eppinger and Kisch[69] consider the subcutaneous tissue to be the principal water depot, we found in obese people that both layers of the cutis—i.e., the stratum papillare and the stratum reticulare—are rich in water and in sodium chloride, while the subcutaneous tissue is definitely poor in water and salt. The pre-edematous condition of the skin, which we were able to demonstrate in chemical studies in the living skin of obese individuals, fully explains the clinical observation that, at the beginning of fluid restriction in the dietary treatment, a loss in weight of 1 to 2 Kgs. is followed by a marked improvement in the condition of the skin. This can be explained only by the fact that the excessive water has been deposited in the cutis proper and not in the subcutaneous tissue.

Moreover, with the aid of the punch-biopsy method we were able to show that there are some skin diseases (notably, certain forms of dermatitis) in which the entire integument, including the clinically normal areas, is in a pre-edematous state; while in other dermatoses (erysipelas, for example) the clinically normal layers of skin present normal water levels (Table 4). It will hardly be necessary to stress here that these findings may be of great significance in the pathogenesis, and possibly also the therapy, of these diseases.

The fact that the apparently normal areas of the skin in dermatitis contains a plethora of water may explain why this disease so commonly

[69] Eppinger, H. and Kisch, F.: Wien. klin. Wchnschr. 38: 299, 1925.

spreads to remote and seemingly healthy skin sites, while erysipelas always spreads slowly and gradually. This leads to certain conclusions as to therapy. If we are confronted with a general disturbance of the water metabolism of the skin, causing an increase in the water content, we must resort to general measures designed to combat the underlying cause. Indeed, Meyer[70] and other investigators, including the present writer, have obtained highly gratifying results by treating such dermatitides with a strict milk-water diet, which drastically flushes out the water and sodium chloride deposits of the skin.

Water should be given in sufficient quantities to provide for both sensible and insensible perspiration, and for the production of sufficient urine to enable the patient to excrete waste products. In this connection, it is pertinent to recall that the daily insensible perspiration in a normal individual amounts to about 500 cc., that the volume of sweat is 300 to 600 cc., and that the daily urinary output averages 1,750 cc. It is generally assumed that the skin normally eliminates about one fourth of the total water output, the balance leaving the body through the urine, feces, and respiration. The best criteria of an adequate intake of liquid are: (1) a twenty-four hour urine cutput of at least 1,000 cc. of about 1.020 specific gravity; (2) a moist tongue; and (3) absence of thirst.

TABLE 4.—*Comparison of Water Content in Apparently Clinically Normal Skin in Dermatitis and Erysipelas*

	Cutis		Subcutaneous Tissue	
	Affected skin	Apparently Normal skin	Affected skin	Apparently normal skin
Dermatitis	80.3	75.7	61.9	21.4
Erysipelas	76.2	64.7	51.5	18.4
Normal individual		61–67		11–20

The problem of the water metabolism of the skin is far more complex than one might expect. It is closely connected with mineral metabolism, with the protein and fat content of the skin, and thus with the diet. In short, the skin plays a predominant role both as a storehouse for water ingested with the food and as an organ engaged in water excretion.

B. MINERAL METABOLISM OF THE SKIN

The presence of minerals is essential for the maintenance of life. The undisturbed course of the various biologic processes can be insured only if the cell and tissue fluids contain adequate amounts of the essential salts. The mineral substances maintain the osmotic pressure, further the diffusion, regulate the exchange of fluids among the cells and tissue juices, and control the vasomotor tone and the conductivity of the nervous system. The following mineral substances are found in the skin: sodium, potassium, calcium, magnesium, chlorine, sulfur, phosphorus, aluminum, iron, zinc, copper, and silicon.

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[70] MEYER, J.: Arch. dermato-syph. de la Clinique de l'Hopital St. Louis 1: 528, 1929; J. de méd. et chir. prat. 109: 628, 1938.

Since the mineral substances are excreted by way of the kidney, skin, and bowel, they must constantly be replenished from the food, in which they are supplied to the organism in the form of cations (ions with a positive electric charge) or anions (ions with a negative charge). In this connection it must be emphasized that the skin, unlike the blood, is capable of storing certain mineral substances, and its supply of these substances is very largely dependent upon the nature of the diet. The dietary influence can be so strong as to lead to an increase (mineralization) or decrease (demineralization) in the quantities of certain mineral substances in the skin and other tissues of the organism, and thus to an appreciable dislocation in this respect (transmineralization). Such changes in the mineral content of the tissues are brought about by unbalanced diets or by the prolonged use of mineral waters. Thus, raw foods will tend to increase the organism's supply of potassium and to decrease the sodium, calcium, and magnesium (Doerffel.[71]) The Sauerbruch-Herrmannsdorfer diet leads to a decline in the chlorine content and a simultaneous rise in the calcium of the diseased skin (Herrmannsdorfer[72]). Partaking of a diet or of mineral waters high in salt bring about an increase in the sodium and chlorine in the skin and a decrease in the calcium, magnesium, and possibly potassium as well.

Luithlen[8] stressed the point that it is by no means enough to determine the quantity of any one mineral ingredient of a tissue, but that it is necessary, in each case, to know the reciprocal relationships between the cations. For the absolute quantity of each one of the substances is not of prime importance: as I. Loeb was the first to demonstrate, the maintenance and undisturbed functioning of the cells is dependent upon a definite balance between these cations. This explains how the functioning of the skin, and indeed of the tissues in general, can be affected by such moderate influences as those resulting from a change in diet which, without any appreciable alteration in the total amounts of the bases present, can cause a shift of the ratios between the several bases. Confirming Luithlen's findings, Hayashi[73] demonstrated that the ratio between K, Na, Ca, and Mg remains almost constant in the skin of rabbits as long as the animals are kept on the same diet, but that the ratio changes considerably when different kinds of fodder are given.

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71. Doerffel, J.: Arch. f. Dermat. u. Syph. **162:** 621, 1931.
72. Herrmannsdorfer, A.: München. med. Wchnschr. **78:** 571, 1931.
73. Hayashi, K.: Jap. J. Dermat. & Urol. **26:** 726, 1926.

To obtain a clear idea of the connection between the diet and the mineral metabolism of the skin, it is necessary to study the skin itself chemically, and not merely the blood or blood plasma. While Na, K, Ca, and Mg are present in the living cell and in its media (blood plasma, lymph) as chlorides, phosphates, sulfates, and carbonates in balanced proportions, the relative ratios of these elements are not the same in the cells as in the media. In the former potassium is the most abundant cation and then, in order, sodium, magnesium, and calcium. On the other hand, in the intracellular fluids of the body there is far more sodium than potassium, and calcium is more abundant than magnesium. The skin's content of mineral substances fluctuates within fairly wide limits, as shown by Table 5. It is to be noted, furthermore, that the calcium content of the skin of carnivorous animals (dogs) is low, and the potassium content high; and that, conversely, the skin of an animal fed green fodder has a high calcium and a low potassium level. This is in all probability due to the differences in the diets. These levels apply to dried skin. Assuming that the average water content of the skin is 66 per cent, the cation content of the fresh skin is approximately one third of that indicated in Table 5.

TABLE 5.—*Normal Values for Minerals of the Skin*
(In Mg. per 100 Gm. of Dried Skin)

	Na		K		Ca		Mg		Author
	Range	Average	Range	Average	Range	Average	Range	Average	
Man	298–408	360	168–339	290	34–59	46	20–38	30	Brown[75]
	273–424	349	194–373	283	18–33	26	23–35	29	Doerffel[76]
Dog	155–250	201	158–395	238	31–58	43	21–37	27	Brown[75]
Rabbit	116–243	181	102–188	148	51–86	74	17–52	35	Brown[75]
	135–201	168	113–180	147	27–39	33	22–39	31	Doerffel[76]

We must mention a fundamental difficulty involved here, namely, that these analyses can serve only to determine the total amounts of mineral substances present. We are not, as yet, equipped to determine what proportions of the minerals exist as ions, which are believed to be the active factor.

The manner in which the various mineral substances in the skin are dependent upon the diet will now be considered, beginning with the cutaneous chlorine content. According to the present writer's investigations,[10] this varies between 200 and 320 mg. per cent in the human skin. The levels reported by Nadel[49] are somewhat higher, 311 to 371 mg. per cent. Rabbit skin shows approximately the same levels (Klauder and Brown[74]).

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74. KLAUDER, J. V. and BROWN, H.: Arch. Dermat. & Syph. 15: 1, 1927.
75. BROWN, H.: J. Biol. Chem. 68: 729, 1926.
76. DOERFFEL, J.: Delib. 9th Internat. Dermat. Congress 2: 186, 1936.

The role of the skin as a depot for sodium chloride is no less important than the part it plays in the water balance of the entire organism. According to Wahlgren,[77] the skin has a higher chlorine content, both relatively and absolutely, than any other organ. Wahlgren[77] and Padtberg[78] determined that when the organism is on a high chlorine diet the skin contains one third of the total chlorine of the body, while on a low chlorine regimen one fourth of the organism's total chlorine is in the skin.

When a high sodium chloride diet is continued for some time, the skin of healthy human beings and animals can, as the present author demonstrated,[10] adjust itself to a higher chlorine level; however, the increase in sodium chloride never exceeds 15 to 20 per cent of its original level. On the other hand, we[10] found that, in all cases of pemphigus and dermatitis herpetiformis (Duhring), oral administration of 10 Gm. of table salt (salt tolerance test) caused the chlorine level in the skin to rise much higher, often as much as 100 per cent. However, chlorine retention in the skin following a high salt intake is not limited solely to the pemphigus group; we have also encountered manifestations of this metabolic disturbance in diffuse erythrodermas, for example. Nevertheless, the fact that the dermatoses which must be taken into consideration in the differential diagnosis of pemphigus, such as bullous dermatitis and the like, show no abnormal increase in the chlorine content of the skin following the administration of 10 Gm. of salt daily, permits us to use the salt tolerance test as a diagnostic aid, notably in incipient pemphigus, including pemphigus mucosae oris. We are inclined to interpret such chlorine retention in the tissues as a sort of defense mechanism on the part of the organism against the highly toxic protein-disintegration products which occur in pemphigus. We recommend, therefore, that this natural defense reaction be supported by small quantities of table salt by mouth, 1 Gm. three times daily in enteric coated tablets, and 1 Gm. five times daily, if the patient is unable to take any food which normally contains salt. We have observed that oral administration of any larger amounts of salt than 10 to 20 Gm. daily almost invariably brought on new showers of pemphigus blisters.

In order to determine the extent of the influence of the salt-poor Sauerbruch-Herrmannsdorfer diet on the chemistry of the skin, the writer[79] studied the chlorine levels of the skin and blood in a series of lupus patients, both before and during the salt-poor regimen. All the patients with skin tuberculosis—and this applies to any cutaneous disease marked by inflammatory processes—showed increased chlorine levels in the blood, and especially in the skin, when on a normal diet. In eleven lupus cases, which had been on a Sauerbruch-Herrmannsdorfer dietary for at least four weeks, there was a decline from the high chlorine levels originally noted, but the figures were still above the normal. Four cases, which were given a special study because of distinct exacerbation of the process after two weeks of this low salt regimen, showed considerably higher chlorine levels at this time. The significance of these findings is limited, however, since our chemical methods determine the total chlorine content; and the salt-poor diet in question aims only to lower the sodium chloride level, and completely disregards the quantities of other chlorides (e.g., potassium chloride). Nevertheless, these studies show that strict adherence to a salt-poor diet for some length of time serves to lower the chlorine levels in the skin.

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[77] Wahlgren, V.: Arch. f. exper. Path. u. Pharmakol. **61:** 97, 1909.

[78] Padtberg, J. H.: Arch. f. exper. Path. u. Pharmakol. **63:** 60, 1910.

[79] Urbach, E.: Arch. f. Dermat. u. Syph. **174:** 1, 1936.

While there can be chlorine retention without corresponding water retention under certain conditions, as in some cases of pemphigus and dermatitis herpetiformis, we found that in the great majority of cutaneous diseases an affected skin site showing a high water level also had a high chlorine content. This is not remarkable in inflammatory cutaneous processes such as dermatitis or erythroderma, but it is certainly surprising to find that ichythyotic or sclerodermatic skins contain extraordinarily high chlorine levels (412 and 343 mg. per cent respectively). To understand this, it must be remembered that in these conditions there are changes in the physicochemical structure of the collagenous and elastic fibers of the cutis, as shown by histologic investigations, notably those of Unna.[80] Schade and Menschel[55] moreover were able to demonstrate that the protein colloids of the connective tissue can, under certain pathologic conditions, hold salts by chemical adsorption quite independent of the water storage capacity. According to Schade, a slight acidotic tendency on the part of the tissue fluids serves to increase the amount of chlorine held by the colloids of the connective tissue. The chlorine content of the cutis is invariably from five to ten times greater than that of the subcutaneous tissue. This is also true of the chlorine retention in obesity, where we[10] found high chlorine levels in the strata papillare and reticulare of the cutis, but almost normal levels in the subcutaneous tissue.

Quite different conditions are observed in the edematous skin of patients with congestive heart failure. In accordance with the marked saturation of the tissues with serous fluid, the water content of the cutis shows an appreciable increase, while its rise in the subcutaneous tissue is extraordinary. Furthermore, the chlorine level in the cutis is so high (509 mg.

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[80] Unna, P. G.: Biochemie der Haut. Jena: Fischer, 1913.

per cent) that it approaches that of the blood, while the amount of chlorine in the subcutaneous tissue is very much less (150 mg. per cent). This shows once again that there exists some degree of independence between salt metabolism and water metabolism; and that other, particularly colloidal chemical, factors may play a role which has not yet been fully explored.

Most investigations dealing with sodium chloride metabolism in the skin have been limited to chloride determinations. As we have explained on page 60, some of the effects of sodium chloride are due principally to the action of the sodium cation and not to that of the chloride anion. Thus, for example, sodium chloride increases the water-holding power of the tissue, while calcium chloride and potassium chloride exert precisely the opposite influence. In diabetics prone to edema, sodium bicarbonate has a strongly hydropic effect and potassium bicarbonate has a contrary action.

Keining and Hopf[81] have suggested that it is not so much sodium *per se* as its disproportionate relationship to other cations in refined table salt which produces deleterious effects in man. This is the result of the process of refining crude salt whereby most of the naturally occurring cations (K, Ca, Mg) are removed, leaving a heavy preponderance of Na. As a substitute for ordinary table salt they suggested the use of a salt mixture (Titro Salt) in which the cations are present in the same physiologic proportions as in the tissue fluids. By this means these authors hoped to produce the same effect as the low salt Sauerbruch-Herrmansdorfer diet without the necessity of subjecting the patient to a regimen made difficult by its very low salt content (see p. 67).

A number of studies seem to reflect the importance of *potassium* metabolism in the skin. In man the normal potassium content varies considerably but averages about 247 mg. per 100 Gm. of dried skin (Nathan and Stern,[82] Brown,[83] Cornbleet et al.[84]), while the potassium in the serum amounts only to 18 to 23 mg. per cent. Stern[85] noted that samples of inflamed skin contained double the normal quantities of potassium. Luithlen found that a diet of oats raised the potassium level of the skin at the expense of sodium, calcium, and magnesium; and Doerffel[71] found the same to be true of the salt-poor Sauerbruch-Herrmannsdorfer diet. Luithlen,[8] Klauder and Brown,[74,86] and Vogt[87] stressed the fact that there is a distinct relationship between cutaneous irritability and certain cations in so far as the former is accompanied by increased potassium and decreased calcium levels in the skin. For some years various authors have claimed that small doses of potassium chloride are of therapeutic value, particularly in allergic dermatoses; however, other investigators, including the present writer, have been unable to substantiate these findings.

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[81] Keining, E. and Hopf, G.: Arch. Dermat. & Syph. **32:** 739, 1935.
[82] Nathan, E. and Stern, F.: Dermat. Ztschr. **54:** 14, 1928.
[83] Brown, H.: J. Biol. Chem. **75:** 789, 1927.
[84] Cornbleet, T., Ingraham, R. C., and Schorr, H. C.: Arch. Dermat. & Syph. **46:** 833, 1942.
[85] Stern, F.: Klin. Wchnschr. **10:** 1944, 1931.
[86] Klauder, J. V. and Brown, H.: Arch. Dermat. & Syph. **20:** 326, 1929.
[87] Vogt, J. H.: Skandinav. Arch. f. Physiol. **77:** 92, 1937.

The study of cutaneous *calcium* metabolism received its chief stimulus from Luithlen's finding[8] that an excess of calcium administered to an animal decreased the skin's reactivity to inflammatory stimuli. Klauder and Brown[85] confirmed the existence of an inverse relationship between the calcium content of the skin and the degree of cutaneous irritability. At the same time they demonstrated in rabbits, as many other authors have demonstrated in man, that the serum calcium level cannot be used as a yardstick for the degree of reactivity of the skin. In other words, the concentration of calcium in the blood is not the only factor controlling calcium metabolism in the skin. These findings show, once again, the futility of studying the chemistry of the blood instead of that of the tissues in certain dermatoses. Doerffel[88] presented evidence that the skin is capable of serving as a storage organ for calcium by acting as a temporary depot between the serum and its main destination, the bones, in which the calcium salts are chiefly deposited.

It is interesting to note that van der Schaaf et al.[89] found that the calcium content of guinea pig skin is reduced by about 10 per cent when table salt is added to a diet rich in calcium. Opposite effects resulted from a salt-free diet.

Surace[90] stated that acutely inflamed skin contains more than the normal amount of calcium, while in areas of chronic cutaneous inflammation the calcium level is lower. However, according to Stern,[83] the inflamed skin also shows elevated values for other minerals, and the changes are therefore not characteristic of any specific inflammatory process.

Disturbances of calcium metabolism in scleroderma, calcinosis of the skin, and other diseases with cutaneous manifestations, as well as their relationship to dysfunctions of the parathyroid glands, will not be discussed here because they do not lie within the province of this book.

The normal *magnesium* values for dried human skin average 30 mg. per cent (Brown[75, 83]). In mineral balance experiments, Luithlen[8] found that there was a relative increase in magnesium (and in potassium and calcium as well), in contrast to a relative decrease in sodium when the animals were put on a green fodder diet. Doerffel[71] noted a decrease in the magnesium content of the skin as the result of a low salt diet. The

[88] Doerffel, J.: Arch. f. Dermat. u. Syph. **174:** 1, 1936.

[89] van der Schaaf, A. T. and von Ormondt, J.: Nederl. tijdschr. v. geneesk. **76:** 148, 1932.

[90] Surace, F.: Dermosifilografo. 7: 255, 1932.

question of the magnesium content of the skin was relatively neglected for many years. However, this mineral has attracted general attention in the past few years, since Kruse et al.[91] showed that magnesium deprivation in young rats led to a disease characterized by muscular hyperexcitability, nephritis, hepatitis, intense generalized erythema and edema of the skin, sometimes also erythema multiforme-like manifestations, and even cutaneous ulcers. Moreover, the spectrographic and micro-incineration studies of Engman, Jr., and MacCardle[92] revealed that chronic disseminated neurodermatitis is characteried by a localized magnesium deficit in the skin, while the magnesium level in the blood remains unchanged. The very fact that in experimental magnesium deficiency in rats there is a decrease of magnesium in the blood (MacCardle et al.[93]) but not in the skin (Sullivan and Evans[20]) shows that the mechanism in disseminated neurodermatitis differs from that of experimental magnesium deficiency. In disseminated neurodermatitis the skin is apparently unable to accept or retain biologically active magnesium although the patient ingests and excretes this element in normal amounts. This example again emphasizes the importance of analyzing the skin, as well as the blood, chemically.

The major part of the cutaneous *sulfur* is contained in the keratin of the superficial layer of the epidermis, known as stratum corneum, while smaller amounts are to be found in the collagen and elastin of the cutis. According to Klauder and Brown,[95] the percentage of sulfur is roughly two and one-half times higher in the scales than in the skin. Human hair and nails have an especially high sulfur content (4.5 to 5.2 per cent and 3.0 to 3.6 per cent respectively). Klauder and Brown[96] also demonstrated that the sulfur content of the skin decreases with age, both in man and in animals, from an average of 0.475 mg. to 0.275 mg. per cent. The sulfur in the skin is essentially in organic combination. It is believed that a large portion is present in the form of cystine and cysteine. Other known sulfhydryl compounds in the skin are glutathione and methionine.

According to more recent investigations, the skin acts as a sulfur depot, on which demands are made as part of the defensive mechanism operative on infections and intoxications. Probably for this reason the sulfur content of the skin is low in patients with lupus vulgaris, pellagra, and in acute and chronic cutaneous infections. It is interesting to note the definitely low percentage of sulfur in the skin of patients with arsphenamine dermatitis (Klauder and Brown[95]). This conforms with the observa-

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91. Kruse, H. D., Orent, E. ., and McCollum, E. V.: J. Biol. Chem. **96:** 519, 1932.
92. Engman, M. F. and MacCardle, R. C.: Arch. Dermat. & Syph. **46:** 337, 1942.
93. MacCardle, R. C., Engman, M. F., and Engman, M. F., Jr.: Arch. Dermat.& Syph. **47:** 335, 1942.
95. Klauder, J. V. and Brown, H.: Arch. Dermat. & Syph. **34:** 568, 1936.
96. Klauder, J. V. and Brown, H.: Arch. Dermat. & Syph. **31:** 26, 1935.

tions reported by Voegtlin et al.,[97] that the effect of arsenic on protoplasm is essentially due to an action affecting certain organic compounds which contain sulfur in the sulfhydryl form. Therefore, Voegtlin[97] and Klauder[95] and their collaborators recommend a high protein diet for patients with toxic reactions due to arsenic, gold, and similar toxic agents. (See high protein diet, p. 118.) In this connection, mention must be made of Voegtlin's experiments[98] on toxicity in rats, in which it was demonstrated that cyanide is detoxified by cystine, cysteine, and glutathione. He expressed the belief that poisons react chemically with the cystine and glutathione in the organism and that detoxification is to be attributed, primarily, to the proper physiologic concentration of these compounds in the tissues, resulting from the addition of an extra supply of sulfur from without.

Strickler and Adams,[99] Klauder and Brown,[95] and others reported a high percentage of sulfur in the scales and skin of patients with psoriasis, a finding which suggests that the sulfur metabolism is abnormal in this disease. The reader is referred to the chapter on psoriasis (p. 448) for a further discussion of this question, as well as for comments on Klauder's suggestion that a low protein diet be given in order to reduce the sulfur content of the skin.

The amounts of *phosphorus* contained in the skin are very small. According to Huebner's experiments on dogs,[100] the organ containing relatively the smallest amounts of phosphorus is the defatted skin. According to Brown,[75, 83] the skin contains 0.041 to 0.085 mg. per cent, the internal organs about 0.2 mg. per cent of phosphorus. It is interesting to note that the phosphorus content of young animals is approximately three times that of adults (McLaughlin and Theis[40]). Similarly, the figures for cutaneous phosphorus in children, as reported by Klose,[50] are considerably higher than the corresponding figures for adults. However, it seems that a high phosphorus diet serves to increase the phosphorus content of the skin, even in adult animals (Huebner[100]).

As to the influence of the diet on the relative quantities of *zinc*, *copper*, *lead*, *manganese*, *iron*, *nickel*, and *cobalt* in the skin, very little can be said with any degree of certainty. According to Rothman and Schaaf,[41] the epidermis ranks first among the tissues in its capacity to take up these elements and to store them in its horny appendages, notably in the hair and feathers. Keil and Nelson,[101] and Gorter[102] claim that a diet deficient

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97. Voegtlin, C., Dyer, H. A., and Leonard, C. S.: Pub. Health Rep. **38:** 1882, 1923.
98. Voegtlin, C., Johnson, J. M., and Dyer, H. A.: J. Pharmacol. & Exper. Therapy **27:** 467, 1926.
99. Strickler, A. and Adams, P. D.: Arch. Dermat. & Syph. **25:** 11, 1932.
100. Heubner, W.: Arch. f. exper. Path. u. Pharmakol. **78:** 24, 1915.
101. Keil, H. L. and Nelson, V. E.: J. Biol. Chem. **93:** 49, 1931.
102. Gorter, F. J.: Ztschr. f. Vitaminforschung **4:** 277, 1935.

in copper tends to bleach the hair pigment of rats. Such depigmentation can be prevented or arrested by administering minute quantities of copper. Yeast, according to Gorter, exerts a similar influence, which he attributes to its copper content.

Although very little is known about the connection between the *fluorine* content of the food and notably of the drinking water and the skin, the influence of the water's fluorine content, hardness, and pH values on dental caries has been quite exhaustively investigated. The conclusions reached in one of the most recent studies (Ockerse[103]) may be summarized as follows: (1) The incidence of caries is very high when drinking water contains much less than one part per million of fluorine; (2) The incidence of caries is lower when the water is hard, and higher when the water is soft. (3) The greater pH (i.e., more alkaline) values of drinking water are significantly associated with a lower caries incidence.

Lastly, the iodine content of human skin must be briefly considered. According to Goyert,[104] human skin contains from 150 to 200 gamma per cent of iodine, rabbit's skin from 300 to 500 gamma per cent. Both figures are definitely above those for the normal blood. Up to the present time no explanation has been offered for the interesting observation that the iodine content of the skin is abnormally high in certain cutaneous conditions, especially in dermatitis herpetiformis (Duhring) and some allergic dermatoses.

C. CARBOHYDRATE METABOLISM OF THE SKIN

A disturbance of the carbohydrate metabolism may be the cause of many different cutaneous symptoms and diseases. As we shall point out in some detail on page 78, merely testing for glycosuria or determining the fasting blood sugar level is not sufficient to exclude the possibility of an underlying diabetes mellitus. Wherever the clinical picture of a dermatosis or the patient's family history suggests the possibility of disturbed tolerance for carbohydrates the sugar tolerance test is indispensable.

Under normal conditions there is a certain parallelism between the skin sugar and blood sugar tolerance curves, with the one difference that the skin sugar curve reaches its maximum later and correspondingly takes longer to return to its original level (see Figs. 20, 21 on p. 78). Under pathologic conditions the skin is capable of retaining more sugar and for a longer period of time than it does under normal circumstances, a fact which is highly significant when one recalls that the skin constitutes 16 per cent of the total body weight and is three times as heavy as the liver.

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[103] Ockerse, T.: South African M. J. **18:** 255, 1944.

[104] Goyert, K.: Arch. f. Dermat. u. Syph. **182:** 190, 1941.

In rare instances, however, there is a discrepancy between the fasting blood and skin sugar levels and between their carbohydrate tolerance curves in that the blood shows normal values while those of the skin are abnormally high. For this condition the present writer[36] has proposed the term "skin diabetes." It is, therefore, essential to carry out skin sugar determinations in all doubtful cases in which the presenting skin disease might possibly be attributable to a disturbance in the carbohydrate metabolism but in which the blood sugar tolerance curve is apparently normal.

Studies on fasting subjects living under similar dietary conditions reveal that the skin of man and that of animals present relatively constant sugar levels (Urbach and Lentz[11]). Table 6 shows that man has the lowest skin sugar value, an average of 58 mg. per cent, while the mean blood sugar level is 94 mg. per cent. The proportion of the skin to blood sugar is about 61.4 per cent.

TABLE 6.—*Level of Free Sugar of Blood and Skin in Man and Animals*

Subject	Sugar Content in Mg. Per Cent		Blood/Skin Sugar ratio in per cent
	Blood	Skin	
Man	94	58	61
Mouse	114	77	67.5
Dog	84	87	103
Rat	85	106	125
Rabbit	105	134	128
Guinea pig	110	145	132
Cat	97	148	151

As we shall presently demonstrate, the individual's dietary habits exert a marked influence in this connection. Thus the present writer found definitely higher figures in Vienna (blood sugar 103 mg. per cent, skin sugar 61 mg. per cent) than in his Philadelphia material. This may unquestionably be explained by the fact that the usual diet in Austria was appreciably higher in carbohydrates.

In animals, with the exception of the mouse, the sugar content of the skin is higher than that of the blood. The highest values for skin sugar are found in guinea pigs and rabbits.

Determination of the quantity of the so-called free sugar does not mean that the entire carbohydrate content of the blood and tissues has been accounted for. The reducing capacity of both shows a marked increase after they have been boiled with an acid. These reducing substances have generally been termed bound sugar. In man, the bound skin sugar is about fifteen times greater than the value for the free cutaneous sugar, and one and one-half times that of the bound sugar in the blood. Urbach and Rejtoe[105] found that when rabbits are kept on various types of diet (green fodder, high carbohydrate diet, mixed diet) those which have been fed large quantities of carbohydrates show considerably greater amounts of bound sugar in the skin than do the animals which have been kept on a green fodder diet. However, there is no demonstrable connection between dermatoses and the bound sugar concentration in blood and skin.

In diabetes mellitus the ratio between skin sugar and blood sugar shifts in favor of the skin. Thus we observed seven diabetics who presented an average fasting blood sugar level of 155 mg. per cent and a skin sugar level of 103 mg. per cent—a ratio of 66.4 per cent.

In cases of mild diabetes it is necessary, as far as fasting skin sugar levels are concerned, to distinguish between two categories: namely, those with and those without skin manifestations. In the former we include notably recurrent furunculosis, axillary sweat gland abscesses, dermatitis, urticaria, and pruritus. Cases with these skin manifestations, though presenting only slightly increased fasting blood sugar levels (average 127 mg. per cent), show a high fasting skin sugar (average 82.8 mg. per cent). Those without cutaneous symptoms reveal only a slight elevation in skin sugar (65.5 per cent) and somewhat higher blood sugar (133 mg. per cent). Therefore, the ratio of the skin sugar to blood sugar is considerably higher in mild diabetics with skin manifestations (65.7 per cent) than in those without cutaneous lesions (49.6 per cent). However, further investigations on a larger group of diabetics will be necessary before our preliminary findings can serve as the basis for explaining why some diabetics are inclined to skin diseases and others are not. Moreover, it will be interesting to discover whether in the group with skin manifestations the skin sugar reacts more slowly to dietary measures than in the other group.

Interesting, too, are the results of studies we carried out on the behavior of the skin sugar following administration of insulin. When we gave animals insulin in doses large enough to bring on severe muscle spasm and death after two hours, we found that the skin sugar and blood sugar curves were fairly parallel, falling steeply at first, then dropping less precipitously. However, the skin sugar could not be depressed below a certain level, even when death was imminent. Tsukada[106] obtained similar results.

We turn now to a discussion of the dependency of the sugar content of the skin on various dietary conditions. The opinion is still widely held that the diet has little if any influence on the fasting blood sugar level. This does not by any means hold true in all cases. In an extensive series of experiments on human subjects and on animals the present writer was able to ascertain that the fasting levels in both the blood and the skin are directly influenced by the carbohydrate content of the diet.

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[105] Urbach, E. and Rejtoe, K.: Arch. f. Dermat. u. Syph. **166**: 478, 1932.

[106] Tsukada, S.: Tohoku J. Exper. Med. **21**: 347, 1933.

Even more clearly evident is the influence exerted by the diet on the behavior of the blood sugar curve, following administration of massive quantities of sugar. Thus Figure 29 (p. 85) shows the response of a patient who had been maintained on a carbohydrate-free diet; a blood sugar of 210 was found thirty minutes after ingestion of 100 Gm. of sugar. When the patient had been fed a mixed diet, a level of only 170 was noted, following the glucose meal (Fig. 28, p. 85). This difference in response can be demonstrated even more strikingly in experiments on animals. For example, when a dog on a diet entirely free from carbohydrates was given sugar, 1½ Gm. per kilogram body weight (Fig. 24 on p. 81), the blood sugar rose to 280 mg. per cent and the skin sugar to 200 mg. per cent, as compared with 140 and 136 mg. per cent respectively when the animal was kept on a strict carbohydrate diet (Fig. 25, p. 81). Similar findings have been reported by Himsworth[107] in man and by Toshima[108] in animals.

TABLE 7.—*Influence of Low Carbohydrate Diet on the Fasting Sugar of Blood and Skin*

Patient	Age	Sex	Disease	After Normal Diet			After Low Carbohydrate Diet (3 Weeks)		
				Blood sugar	Skin sugar	Ratio	Blood sugar	Skin sugar	Ratio
M. W.	45	f	psoriasis	104.2	63.4	60.8	90.3	55	60.9
H. B.	44	m	furunculosis	113	69.4	61.4	86.8	53.8	61.9
A. W.	38	m	epidermophytosis	113.2	68.1	60.1	93.2	57.8	62.0
S. B.	30		xanthoma	111.2	64.4	59.3	97.1	59.8	61.6
W. M.	70	m	epithelioma	105	63.5	60	86.9	53.7	61.7

The dependency of the sugar level of the skin upon the nature of the diet readily explains the efficiency of a low carbohydrate diet in diabetic dermatoses.

Furthermore, investigations by Tsukada[106] disclose the very interesting fact that not only the carbohydrate content of the diet but also its acid and base constituents exert a definite influence on both the sugar level and sugar tolerance of the skin, while the blood sugar is more or less independent of the acidity or alkalinity of the food. For example, in animals fed on oats or cabbage the skin sugar shows appreciable fluctuations while the blood sugar remains virtually constant in almost all cases. The skin sugar tolerance is increased by an acid ash diet (oats) and decreased by alkaline ash food (cabbage).

[107] HIMSWORTH, H. P.: Lancet **2:** 1, 1939.

[108] TOSHIMA, E.: Jap. J. Dermat. & Urol. **36:** 405, 1934.

A diet high in fats results in a distinct decrease in the sugar content of the skin while that of the blood remains practically stationary (see p. 95).

For years the present writer[11] has been championing the concept that the skin not only serves as a temporary storehouse for dextrose, but also plays an important role in the intermediary carbohydrate metabolism. Here we should like only to summarize the facts in support of this thesis: (1) the high levels of free and bound sugar in the skin of animals; (2) the demonstrable presence of cleavage and end products of the intermediary carbohydrate metabolism in the skin; (3) the capacity of the skin to transform glucose into glycogen; (4) the presence of glycolytic ferments in the skin; and (5) the fact that insulin-like substances can be derived from the skin.

Finally, the concept of "skin diabetes" or "independent cutaneous glycohistechia" will be discussed in some detail. This term was suggested by the writer[36] to serve as a designation for the syndrome of a therapy-resistant skin disease (generally presenting the clinical picture of furunculosis, sweat gland abscesses, dermatitis, or pruritus), high fasting skin sugar level together with a normal blood sugar curve, and marked improvement of the dermatosis, as well as a fall in the high skin sugar level, on a low carbohydrate diet, sometimes combined with insulin.

The following points of evidence lend support to the view that there is a connection between this clinical syndrome and a disturbance in the carbohydrate metabolism, as in diabetes: (1) the high fasting skin sugar level; (2) the pathologic and characteristic diabetic course of the skin sugar curve (Fig. 28, p. 85) following a sugar meal; (3) return to normal of the fasting skin sugar level, as well as of the skin sugar tolerance curve after a low carbohydrate diet, notably in combination with insulin; (4) the decided improvement of the skin disease following the institution of diabetic management without local therapy.

The evidence tending to negate a connection with a true pancreatic diabetes is (1) the virtually normal behavior of the blood sugar tolerance curve and (2) the fact that it has never been possible to demonstrate that a case of this kind has progressed to frank diabetes.

While this question cannot be settled on the basis of our present knowledge we believe that in cases presenting independent cutaneous glycohistechia and apparently normal blood sugar regulation, in short hyperglycodermia without hyperglycemia, there is a disturbance of the carbohydrate metabolism involving only the tissues of the skin. This pattern of behavior may be succinctly described by the term "skin diabetes."*

* Greek: *γλυκύς* = sweet, *ἱστίον* = tissue, *ἔχειν* = to hold.

D. LIPID METABOLISM OF THE SKIN

The term "lipid" will be used in the present discussion to designate the fatty substances in general, as suggested by Bloor.[109] The lipids may be subdivided into (1) simple lipids (chiefly neutral fats and waxes); (2) compound lipids (of which the phospholipids, such as lecithin and cephalin, are the most important in the pathologic chemistry of the skin); and (3) the derived lipids (including cholesterol and the fatty acids).

The question of the distribution of lipids in the skin of man and animals has, to date, received very little attention. Table 8 presents the levels for normal human skin and subcutaneous tissue as determined by Urbach, Epstein, and Lorenz[110] and for blood. Eckstein and Wile[111] analyzed exfoliated scales of skin and found them higher in cholesterol (up to 1.5 per cent) than in the epidermis of normal individuals (0.58 to 0.76 per cent). Roffo[112] investigated the cholesterol content of the skin in various parts of the body and noted far greater quantities of cholesterol in the exposed parts (face) than in the unexposed parts (abdomen). Exposure to sunlight (Roffo[112]) increases the cutaneous cholesterol content. Roffo further reported the interesting observation that there is a definite relationship between the cholesterol content of a given skin area and its predisposition to tumors. Engman and Kooyman[113] found that the fatty substances

TABLE 8.—*Values for Lipids in Skin, Subcutaneous Tissue, and Blood Plasma*

	Mg./100 Gm. of Fresh Skin (Urbach et al.[110])	Mg./100 Gm. of Subcutaneous Tissue (Urbach et al.[110])	Mg./100 cc. of Blood Plasma
Total lipids	1,234	7,523	570–820
Neutral fats	989	7,366	150–160
and			
Fatty acids			200–420
Total cholesterol	245	157	160–250
Combined cholesterol	160	96	110–170
Free cholesterol	85	61	40– 80
Phospholipids			190–200

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109. BLOOR, W. R.: Biochemistry of the Fatty Acids and Their Compounds, the Lipids. New York: Reinhold, 1943.

110. URBACH, E., EPSTEIN, E., and LORENZ, K.: Arch. f. Dermat. u. Syph. **166:** 243, 1932.

111. ECKSTEIN, H. C. and WILE, U. J.: J. Biol. Chem. **69:** 181, 1926.

112. ROFFO, A. H.: Néoplasmes **7:** 344, 1928.

113. ENGMAN, M. F. and KOOYMAN, D. J.: Arch. Dermat. & Syph. **29:** 12, 1934.

on the surface of the skin, which originate in the sebaceous glands, sweat glands, and epidermal cells, contain large amounts of free fatty acids. They expressed the opinion that the latter may well explain the bactericidal capacity of the skin. The lipids have also been studied in the fresh skin of steers by Koppenhoefer[114] and in the skin of cats by Matthews and associates.[115]

As for pathologic conditions of the skin, Marchionini[116] established that the cholesterol content of some skin areas (hairy scalp, cheeks, armpits) was normally high in patients of seborrheic habitus. In cats with experimental diabetes Matthews[115] found transference of neutral fat from the skin and muscles to the liver, as well as increased phospholipid and cholesterol content in the skin and decreased cholesterol in the liver.

However, Milbradt's investigations[117] have shown that extensive inflammations of the skin are also capable of disturbing the fat metabolism. Thus, a milkiness of the serum can clearly be seen coincidental with a croton oil dermatitis, due to the increase in lipids. The phosphatide levels show the greatest rise, then the total fats. While the total cholesterol shows the smallest increase, there is a shift in the cholesterol ester—free cholesterol ratio so that the latter increases at the expense of the former. This change in the ratio led Milbradt to the conclusion that the cutaneous inflammation produces a hepatic disturbance.

Although many contradictory reports have appeared concerning the influence of the diet on serum cholesterol, most investigators are of the opinion that the character and quantity of the food ingested, whether taken over long or short periods, have little effect on the fasting blood cholesterol level (Weinhouse[118]).

Walter and Obtulowicz[119] examined the lipid content of the skin and blood of rats under a variety of dietary conditions. While the cholesterol levels in the blood were found to decline on a fat-free diet, such a regimen exerted no demonstrable influence on the various lipoid fractions in the skin. However, quite different conditions seem to exist in patients with lipoid diseases, notably of the skin. In the section on xanthomatosis we shall discuss the beneficial effects of a diet free of animal sterols as recommended by Schoenheimer[120] and Thannhauser,[121] and present our own investigations, which show that under certain dietary conditions some of the lipoid fractions in the blood are unquestionably changed and the pathologic cutaneous manifestations simultaeously show definite clinical improvement.

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[114] Koppenhoefer, R. N.: J. Biol. Chem. **116:** 321, 1936.

[115] Matthews, V. J., Newton, J. K., and Bloor, W. R.: J. Biol. Chem. **108:** 145, 1935.

[116] Marchionini, A.: Giorn. ital. de dermat. e sif. **78:** 463, 1937.

[117] Milbradt, W.: Arch. f. Dermat. u. Syph. **169:** 494, 1934.

[118] Weinhouse, S.: Arch. Path. **35:** 438, 1943.

[119] Walter, F. and Obtulowicz, M.: Dermat. Wchnschr. **108:** 300, 1939.

[120] Schoenheimer, R.: Ztschr. f. klin. Med. **123:** 749, 1933.

[121] Thannhauser, S. J.: Klin. Wchnschr. **13:** 161, 1934.

The manner in which soy bean lecithin influences the blood cholesterol is worthy of special note. It has been observed that experimental hypercholesterolemia in rabbits (Kesten and Silbowitz[122]) and pathologic hypercholesterolemia in man (Gross and Kesten[124]) can be reduced by the administration of soy bean lecithin; and that this substance also exerts a beneficial effect on xanthomatosis of the skin (Adlersberg and Sobotka[123]). It is now generally believed that it is the choline in lecithin to which these results may be ascribed. The question as to whether or not psoriasis is a disease somehow connected with faulty fat metabolism is still highly controversial, but observations reported by Gross[124] and Goldman[125] and their collaborators would seem to indicate that soy bean lecithin exerts a favorable influence on the clinical manifestations of this disease. However, Goldman has found that the combination of a low fat diet plus soy bean lecithin was more effective than soy bean lecithin given in connection with a regular diet.

E. PROTEIN METABOLISM OF THE SKIN

From the viewpoint of metabolism we must regard food proteins as mixtures of the amino acids into which they are split in digestion. At present the structure and physical and chemical properties of some amino acids are known. Those which the body apparently cannot synthesize are called indispensable or essential. Different amino acids are essential for different species and ages. In adult human beings the nitrogen balance becomes negative if the mixture of amino acids supplied does not include lysine, tryptophan, tyrosine, methionine, leucine, isoleucine, valine, and threonine (Holt and associates[126]).

It is now possible to follow the metabolism of amino acids given as food. By synthesizing them with radioactive nitrogen in the amino group and heavy hydrogen in the aliphatic chains, Schoenheimer and associates[127] have shown that there is a continual process of exchange in which amino acids absorbed from the intestine are incorporated as such into the proteins of the tissues, particularly of the skin, or amino groups are exchanged between tissue protein and absorbed amino acids.

The total nitrogen content of the human skin amounts to 3.5 to 4.5 per

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122. Kesten, H. D. and Silbowitz, R.: Proc. Soc. Exper. Biol. & Med. **49:** 71, 1942.

123. Adlersberg, D. and Sobotka, H.: J. Mt. Sinai Hosp. **9:** 955, 1943.

124. Gross, P. and Kesten, B.: Arch. Dermat. & Syph. **47:** 159, 1943.

125. Smith, C. C., Goldman, L. and Fox, M. H.: J. Invest. Dermat. **5:** 321, 1942.

126. Holt, L. E., Albanese, A. A., Brumback, J. E., Jr., Kajdi, C., and Wangerin, D. M.: Proc. Soc. Exper. Biol. & Med. **48:** 726, 1941.

127. Schoenheimer, R., Ratner, S, and Rittenberg, D.: J. Biol. Chem. **130:** 703, 1939; **134:** 653, 1940.

cent (Urbach,[12] Prokoptschuk and Kurako,[128] Santori[129]). Thus the cutaneous nitrogen level is even higher than in the organs richest in protein, such as muscles (3.4 per cent) and liver (2.8 per cent). Similar conditions prevail in the skin of animals (Stockhausen[130]). This high cutaneous protein content can probably best be explained by the fact that, of all the organs, the skin is made up of tissue structures very high in protein, such as collagen, elastin, and keratin. However, in chemical studies of this kind great care must be taken to remove all hair, since it would constitute a major source of error because of its high percentage of protein.

The principal protein components of the skin are albumin, globulin, mucin, keratin, elastin, collagen, and melanin (Wilson[131]). Keratin occurs almost exclusively in the epidermis and its appendages. Melanin will be found in appreciable quantities only in more deeply pigmented human beings and animals. Table 9 shows the proportions of the various protein components of the skin of steers, cows, and calves (according to McLaughlin and Theis[40]).

TABLE 9.—*Comparison of the Various Proteins of the Skin in Steer, Cow, and Calf* (Expressed as Percentage of Protein in Fresh Cutis. McLaughlin and Theis[40])

	Steer	Cow	Calf
Albumin and globulin	0.70	0.37	1.87
Mucin	0.16	0.13	0.23
Elastin	0.34	0.10	0.02
Collagen	33.20	32.16	30.80

The precise manner in which the proteins of the skin, particularly the ratio between albumin and globulin, are altered in nutritional protein deficiency has apparently not yet been determined. However, conditions in the blood would seem to warrant the conclusion that very important changes do take place. In nutritional edema due to an insufficiency of protein in the diet, the hypoproteinemia is caused principally by a reduction in the albumin fraction, the globulin remaining more or less unchanged. According to Youmans,[132] the standard normal values in the United States are as follows: total proteins 6.0 to 8.0 Gm. per 100 cc. of blood plasma, albumin 4.0 to 5.5 Gm. per 100 cc., and globulin 1.4 to 3 Gm. per 100 cc. The relationship between these two components, the so-called albumin-globulin ratio, is normally about 2.5 : 1. However, variations in this ratio are in themselves of little significance unless it is known whether the changes are due to increases or decreases in either the albumin or the globulin. In other words, the actual values for albumin and globulin are more significant than the ratio between them. As discussed at some length on page 118, protein deficiency can be due to a variety of causes. If a given case is one of nutritional deficiency it can readily be managed by the administration of protein containing the essential amino acids, animal protein being of particular value.

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[128] PROKOPTSCHUK, A. and KURAKO: Arch. f. Dermat. u. Syph. **174:** 525, 1936.

[129] SANTORI, G.: Nitrogen Metabolism of the Skin. Rome: Editr. studium, 1933.

[130] STOCKHAUSEN, J.: Biochem. Ztschr. **22:** 244, 1909.

[131] WILSON, J. A.: The Chemistry of Leather Manufacture. New York: Chemical Catalog Co., vol. 1,1928.

[132] YOUMANS, J. B. and PATTON, E. W.: Nutritional Deficiencies. Philadelphia: Lippincott, 1941.

As to the chemical structure of the cutaneous proteins and the influences which control their composition and variations, we have only in recent years been enlightened by the investigations of biochemists and chemists in the leather industry. These studies have to date disclosed the presence of twenty amino acids (Wilson[131]). In the human skin the presence of the following amino acids has been ascertained: arginine, lysine, histidine, cystine, tyrosine, and tryptophan (Eckstein[133]). The great interest along these lines shown by the chemists of the tanning industry and by biochemists promises to disclose additional information of value.

TABLE 10.—*Normal Limits of Variation of Total Non-protein Nitrogen and Its Fractions in Blood and Skin of Man*

	Blood Serum mg. per cent	Skin mg. per cent
Total non-protein nitrogen	20–40	63–84
Urea nitrogen	10–13	6–11.5
Uric acid nitrogen	1–1.5	1–1.3
Creatinine nitrogen	0.4–0.7	0.4–0.6
Creatine nitrogen	1.0–1.5	1.1–1.6
Free amino acid nitrogen	6–8	17–31
Combined amino acid nitrogen	1–3	20–51
Water	90–91%	62–66%

Until recently very little attention was given to the nonprotein nitrogen of the skin. This term refers to a complex mixture of organic and inorganic nitrogenous compounds which remain in the blood and tissues after the protein bodies are precipitated. Most important of these soluble degradation and disintegration products of protein are urea, uric acid, creatine, creatinine, indoxyl, amino acids, ammonia and its salts, and a number of indefinable nitrogenous substances called undetermined nitrogen. Table 10 presents a summary of the total nonprotein nitrogen and its fractions in blood and skin in man. The total nonprotein nitrogen serves as an excellent index not only of the functioning of the kidneys, but indeed of that of the organism as a whole. We know for instance that the amount of nitrogenous substances in the blood and the tissues can be increased in two ways: (1) by abnormal retention as in nephritis, or (2) by increased formation of soluble nitrogenous products of protein splitting such as follows excessive ingestion of meat, during starvation and in cachexia.

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[133] ECKSTEIN, H. C.: Proc. Soc. Exper. Biol. & Med. 32: 1573, 1935.

According to the writer's own investigations,[12] the nonprotein nitrogen content of normal skin is between 63 and 84 mg. per cent. Similar figures are given by Nadel[49] as well as by Prokoptschuk and Kurako.[123] Figures as high as 250 to 400 per cent have been noted in acute and chronic nephritis by Urbach[11] and Kaplansky.[134] The skin is second only to the muscle tissue in ability to store nonutilizable protein residues, such as uric acid, creatinine, and indoxyl, which once again demonstrates the important role of the skin as a storage place for all manner of metabolic products. Since the skin accounts for approximately 16 per cent of the total body weight, this constitutes a considerable proportion of the organism's total nitrogen storage. Under pathologic conditions, this may perhaps be the cause of the severe itching which so frequently accompanies chronic nephritis: the sensitive nerve endings in the skin may be irritated by the increased retention of certain intermediary protein by-products.

Very little work has been done with regard to the influence of the diet on the nonprotein nitrogen content of the skin. Investigations of the present author[12] in dogs revealed a striking increase in the cutaneous amino acid nitrogen content on a high protein diet, and a definite decrease when a low protein diet was fed. Regarding the other components, there was no change in the levels of uric acid, creatine, and creatinine, but an appreciable rise in urea in the skin on a high protein regimen.

The writer has demonstrated[135] that patients with senile pruritus had as much as double the normal amount of nonprotein nitrogen in the skin, while the level in the blood was normal, and the most painstaking examination failed to reveal any internal or external cause for the itching. Moreover, no such rise in the nonprotein nitrogen level in the skin can be found in aged persons not suffering from pruritus. It is noteworthy that the nonprotein nitrogen retention takes place chiefly in the upper layers of the skin, namely, in the stratum papillare.

What is the significance of the high nonprotein nitrogen level in the cutaneous tissues in senile pruritus? Since the kidneys seemed to be functioning normally in all these cases, the increase in the nonprotein nitrogen content may be explained: (1) as a result of a moderately accelerated, but continuous, disintegration of protein in the aging tissues; (2) as an expression of increased accumulation of protein products, due to the fact that the breakdown of protein is not sufficiently rapid and above all not complete enough in senescence; or (3) as an expression of increased retention of nonprotein nitrogen residues brought about by chemical changes in the colloids of the skin in advanced age.

134. Kaplansky: Biochemistry of the Skin. Moscow, 1931.
135. Urbach, E.: Arch. f. Dermat. u. Syph. **163:** 74, 1931.

CHAPTER II

Influence of Diet on Metabolism of the Skin

The nature of the diet has a profound and direct effect on the metabolism of the skin, as shown in some detail in the preceding chapter. Moreover, it unquestionably exerts a strong influence on the biologic reactivity of the skin. The ingested food can either heighten or lower the tendency of the skin to inflammation, enlarge or diminish its susceptibility to infection, increase or decrease its ability to become allergically sensitized, and intensify or reduce its photosensitivity.

The diet can also affect the skin indirectly by way of the endocrine glands, and can thus influence the resorptive capacity of the tissues, the healing of inflammatory conditions, and indeed all the biologic functions of the skin, including its efficacy as an organ of immunity. When thyroid gland secretion is diminished, the metabolic processes of the skin undergo considerable change. As Eppinger has shown, the resorptive processes are extraordinarily slow in the skin of myxedematous animals and human beings. Luithlen demonstrated that ordinary irritations such as abrasions, which disappear entirely in normal subjects, lead to scar formation in animals whose thyroid gland has been removed. Moreover, it is well known that the activity of the thyroid gland is directly related to the nature of the diet. The thyroid gland is generally small in individuals on a relatively high iodine diet, for example, at the seacoast where quantities of fish and seafood are readily available. We learned in World War I that undernourishment of man and animal can bring about extensive changes in the thyroid and adrenal glands. For example, German pharmaceutical houses found that the extract derived from the thyroid gland of underfed sheep was definitely inferior in quality, and that it was impossible to derive any adrenalin at all from the adrenal glands of these animals. It is logical, therefore, to assume that there must be some etiological connection between the food ingested and the activity of an organ, that in the present case being the skin.

Food *per se* is capable of causing skin diseases in a number of different ways: (1) The nutrient may be spoiled or may contain toxic substances which are absorbed into the organism and then have a deleterious effect on the skin. However, since spoiled food generally causes gastrointestinal disturbances as well, it is often difficult to determine whether the intestinal reaction and the skin manifestations are parallel expressions of the response to the noxious substances ingested, or whether the primary gastrointestinal disturbance promotes the resorption of the substances which exert a toxic effect on the skin. (2) The aliment may be a nutritive allergen to which the patient is hypersensitive. (3) Certain foods can produce digestive disturbances of various types which result in abnormal partial-digestion products. When these are absorbed they may exert irritating effects directly as they circulate through the capillaries and as they are excreted through the skin. (4) Alcohol, coffee, and tea act on the skin through their effects on the nervous system and on the circulation. (5) The food may contain certain elements, such as iodides and bromides, which act in the same manner as when they are ingested in the form of the respective drugs.

Just how the diet exerts its influence on the skin cannot, as yet, be fully explained. In the following pages an attempt will be made to summarize our present knowledge of the subject, specifically with regard to some of the more important forms of diet. We shall first review briefly the principal types of dietotherapy.

1. *Restriction Diet.* When the skin retains abnormal quantities of water (as in acute dermatitis), sugar (as in carbuncles), cholesterol (as in xanthelasma), or uric acid (as in gouty dermatitis), limiting these substances in the diet relieves the skin of their pathologic effects.

2. *Alteration* (Umstimmung) *Diet.* A sudden and drastic change in the individual's dietary will often serve as a stimulus activating the healing processes. This would seem to explain the gratifying results achieved by means of different nutritional approaches in similar skin conditions; for the one thing these dissimilar diets have in common is that they invariably represent a sharp divergence from that to which the patient has long been accustomed. They include the rice diet, milk diet, fruit juice diet, raw food diet, low sodium chloride diet, acidifying and alkalinizing diets, the so-called zigzag diet of von Noorden, the thirst diet of Schroth, and, as the most drastic, the fasting diet. In the zigzag diet, for example, the patient is put on a regimen entirely free of animal protein for two days, immediately after which he goes to the other extreme and takes large quantities of meat. Then there is another abrupt change to a completely salt-free diet, and so on.

3. *Addition or Supplement Diet.* By supplying ingredients which have been lacking or inadequately represented in the patient's customary diet, skin diseases can be combated, especially when attributable to hypovitaminoses, avitaminoses, and protein deficiencies such as famine edema.

4. *Elimination Diet.* In a given case of skin disease due to food allergy the exclusion of the allergenic aliments is obviously fundamental.

Let us now consider in detail the principal forms of diets which are employed as therapeutic measures and particularly their effects on the biologic reactions of the skin. Faulty diets resulting from economic or other social causes as well as those due to disease will be discussed in Part Two, "Nutritional Cause of Dermatoses."

A. ACIDIFYING AND ALKALINIZING DIETS

Luithlen[6-8] was the first to show, in experiments on rabbits, that a diet consisting exclusively of oats, with its preponderance of anions over cations, is an acidifying form of diet and increases the reactivity of the skin to inflammatory stimuli. Conversely, a diet of green fodder has an alkalinizing effect and serves to reduce the reactivity of the skin. Luithlen found that the administration of acid by mouth also increases the skin's reactivity, while the ingestion of calcium salts reduces the intensity of exudative processes. He attributed the change in the degree of cutaneous reactivity to external stimuli to a disturbance in the anion-cation balance of the skin, since he was able to demonstrate that there is a relative increase in potassium and decrease in calcium, magnesium, and sodium on a diet of oats alone. On a diet of green fodder the balance swings toward calcium and magnesium and away from sodium and particularly from potassium. However, Luithlen stressed the point that the ratio of one cation to another, especially the K-Ca ratio, is of greater importance than the quantity of any single cation.

Luithlen's experiments exemplify the fact that any unbalanced diet, even one which is rich in calcium, can upset the acid-base balance. He found that on a diet consisting exclusively of green fodder, which is rich in calcium, and distilled water rabbits seemed perfectly healthy for a short time, then rapidly lost weight, showed symptoms of cachexia, and ultimately died. On examination the tissues revealed a profound disturbance in the ratios of the various mineral substances, as illustrated by a marked loss of sodium. He found, however, that when an animal, which had already lost as much as one third to one half of its body weight on a strict green fodder diet, was continued on the same diet with the addition of generous quantities of table salt in the distilled water, the animal soon recovered. Thus even a diet rich in calcium upsets the acid-base balance and leads to manifestations of disease, provided that there is an inadequate supply of the other basic minerals.

Luithlen's findings, that a diet of oats increases the reactivity of the rabbit's skin to inflammatory stimuli and that a diet of green fodder has the opposite effect, have been almost unanimously confirmed (Klauder and Brown,[136] Hayashi,[137] Negishi,[138] Doerffel,[71] Vogt[87]). The majority

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136. Klauder, J. V. and Brown, H.: Arch. Dermat. & Syph. **11:** 283, 1925.
137. Hayashi, K.: Jap. J. Derm. **26:** 721, 1926; Jap. J. M. Sc. Tr. Dermat. **1:** 95, 1927.
138. Negishi: Jap. J. Dermat. & Urol. **27:** 1, 1927.

of reinvestigators have agreed with Luithlen that on a diet of oats rabbits show a higher cutaneous potassium/calcium ratio than they do on a diet of green fodder. However, in contrast with Luithlen's opinion, Vogt[139] claims that this ratio has no decisive influence on skin irritability. He presented experiments which demonstrated that while acidifying diets increase skin irritability in comparison to alkalinizing diets, neither of these influences the K-Ca ratio and the potassium content of the skin in the same manner as the oat and green diets. He concludes that the variance in action of the two last-mentioned diets is due to the difference in their influence on the acid-base balance proper.

We shall presently give a number of examples to show that acidifying and alkalinizing diets are of special importance in their influence on certain pathologic cutaneous processes. To understand the manner in which these diets act and thus to be in a position to make the best possible therapeutic use of them, it is necessary to discuss them in some detail.

The terms "acid" and "alkaline," as used to describe a given food item, may refer either to the taste of the food, to the reaction of the ash, whether acid or alkaline, or to its biologic effect. These three factors are by no means necessarily interdependent.

The taste of a food can never be relied upon to determine whether it is acid or alkaline. Orange, grapefruit, sour cherries, and sorrel, for example, have an "acid" taste because they contain an abundance of organic acids and are therefore generally regarded as "causing too much acid." But fruit of this kind actually has an alkaline effect on the organism, since the organic acids are transformed into carbonic acid by the metabolic processes, the carbonic acid is eliminated through the lungs, and an appreciable residue of inorganic alkaline material is finally retained in the organism.

Classification according to ash reaction,* on which Ragnar Berg[140] based his extensive tabulation of the mineral contents of foodstuffs, is not wholly dependable. The anions and cations of fruits and vegetables are subject to wide variations, depending upon the conditions under which those aliments have been grown (nature of the soil, fertilizer, cultivation), on the manner in which they are preserved, and on the manner in which they are cooked (Kroetz[141]). Thus, according to Berg[140] vegetables with an original reaction which is decidedly alkaline can become acid after prolonged boiling.

The question as to whether a given salt has an acidifying or alkalinizing effect on the organism is in some part determined by the nature of the food previously ingested. According to Straub,[142] sodium chloride and calcium bicarbonate have an acidifying effect and sodium bicarbonate and calcium chloride have an alkalinizing effect in individuals on a milk diet, while these same salts exert a diametrically opposite influence when the diet consists of potatoes.

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* A nutrient is properly regarded as acid when its residue, after having been metabolized, shows a preponderance of acid equivalents; and as alkaline when its residue has an excess of basic equivalents.

139. Vogt, J. H.: Acta med. Scandinav. (Suppl.) **116:** 1, 1941.
140. Berg, R.: Die Nahrungs- und Genussmittel. Dresden: Pahl, 1925.
141. Kroetz, C.: München. med. Wchnschr. **76:** 1788, 1929.

Individual aliments and diets in general can be accurately classified as acidifying or alkalinizing only according to their biologic effects, the simplest test being the influence of the food on the urinary reaction.*

A preponderantly acid or alkaline diet does not necessarily alter metabolism in the corresponding direction. Nor does the presence of definite evidence of an acidifying or alkalinizing influence, such as the reaction of the urine, inevitably justify the conclusion that a given diet is predominantly acid or alkaline. Therefore Kroetz[141] felt the necessity for introducing the terms "acidifying diets" and "alkalinizing diets" in order to stress the biologic effect of a dietary. We are in agreement with Kroetz that this terminology is preferable to that of acid-ash diet and alkaline-ash diet for the reasons given above. The biologic effect of a given food or diet is the true criterion and the very foundation of this entire therapeutic approach.

Let us now discuss the cardinal question whether a diet having an acidifying or an alkalinizing influence can alter the pH and, therefore, the actual reaction of the blood and the tissues.

The actual reaction of the blood, as determined by the hydrogen-ion concentration or, in other words, the acid-base balance, is a biologic constant. While this constant can be momentarily shifted somewhat in one direction or the other by various biologic processes, the normal balance is promptly re-established by means of a very complex regulatory mechanism.† Thus, acid or alkaline foods can change the absolute amounts of free and bound carbonic acid in the blood but cannot influence the ratio between them. Therefore, a new and radically different diet, even when continued for many weeks, cannot bring about a change of the actual reaction of the blood. On the other hand, the alkaline reserve of the blood—i.e., the normal excess of basic over acid ions—can be affected by the nature of the diet. An acidifying diet tends to lower the alkaline reserve, and an alkalinizing diet has the opposite effect.

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* A strongly acidifying tendency in the diet is indicated by a decline in the pH of the urine and by an increase in its titrable acidity and ammonia content; an alkalinizing tendency, by a rise in the urinary pH and by a fall in its titrable acidity and ammonia content.

† The principal organic buffers are the plasma proteins of the blood, which, because of their amphoteric properties, combine equally well with acids and bases. In addition the organism eliminates acid and basic metabolites through the lungs and kidneys. The kidneys excrete such quantities of acid and base as are necessary to maintain the acid-base balance in the blood and tissues. By varying the respiratory rate and volume, thereby readily controlling the elimination of volatile carbonic acid, the organism can almost immediately reduce an acid surplus or reduce a basic surplus by respectively lowering or raising the bicarbonate level. Furthermore, the liver and the kidney also exercise a regulatory function in this respect. For example, in the presence of excessive acid formation in the tissues and a corresponding lack of base in the blood, the liver does not transform the ammonia derived from protein into urea but uses the ammonia to neutralize the acids.

142. Straub, H.: Therap. d. Gegenw. **70:** 481, 1929.

The level of the alkaline reserve reveals a shift of the acid-base balance of the blood before the actual reaction of the arterial blood shows any change. The importance of the alkaline reserve level is illustrated by the following animal experiments. Rabbits on an alkalinizing diet of turnips, which provide them with a high alkaline reserve, survive without any unfavorable reaction when acid is injected into the blood stream. Yet rabbits on an acidifying diet of oats, thus having low alkaline reserve, die after intravenous administration of the same quantities of acid.

Although the actual reaction of the blood is practically constant, this does not mean that the metabolic processes in the tissues cannot be strongly influenced both by the total mineral content of the diet and by the ratio between bases and acids ingested, as animal experiments have shown. For the tissues, to a far greater extent than the blood, serve as a storehouse for both inorganic and organic surplus material. However, not all tissues are equally qualified for this function; the skin is outstanding in this respect (Urbach[27]). By means of the wheal method of Leszczynski, Lohmar[143] was able to demonstrate that the acid-base balance of the skin can be affected by an unbalanced diet, as shown by a change in the pH of the skin. This method depends on the color change of red (acid) litmus in an alkaline medium. It was found that an alkalinizing diet shifted the pH of the skin to the basic side, while a fasting diet demonstrably exerted an acidifying influence. Cottini[144] showed that ingestion of alkaline or acid substances is followed by a definite shift of the pH of the sweat to the alkaline (up to pH 8.4) and acid (up to pH 4.5) sides, respectively. The pH of the urine shows similar changes.

According to the investigations of Kaplanski and Tolkatschewskaja,[145] as well as of Hayashi,[137] changes of the acid-base balance of the blood in animals do not necessarily involve parallel shifts in the tissues. In fact, the two changes can very well be in opposite directions. Therefore, the result of an examination of the blood alone does not warrant any conclusion as to the state of the acid-base balance in the tissues.

A shift of the acid-base balance to either the acid or the alkaline side

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143. Lohmar, H.: Beeinflussung der Haut Durch Diätengepruft mittels der Lakmusquaddel Methode. Dissertation. Cologne: 1938.

144. Cottini, G. B: Giorn. ital. di dermat. e sif. **75:** 1239, 1934.

145. Kaplanski, S. and Tolkatschewskaja, N.: Ztschr. f. d. ges exper. Med. **63:** 90, 1928.

is of definitely practical significance to the physician, as studies during the past few years have shown. Thus, Schreus[146] succeeded in curing certain cases of urticaria by correcting an acidotic tendency by means of an alkalinizing diet supported by administration of alkalies. Marchionini and Ottenstein[147] successfully managed a case of sweat urticaria by instituting a suitable diet to re-establish the normal acid-base balance. Zitzke and Peters[148] obtained gratifying results with alkalinizing diets in cases of dermatitis. In generalized dermatitides as well as in occasional cases of circumscribed dermatitis, all of which had been refractory to all forms of local therapy, Marchionini,[149] Spillmann, Watrin and Verain, and other authors occasionally obtained impressive results with either acidifying or alkalinizing diets, supported by acid or alkaline medication, as the occasion demanded. Vogt[139] recommends an alkalinizing, low sodium diet for the treatment of conditions in which the organism responds too strongly to different stimuli, as in allergic skin diseases or exudative dermatoses. Local torpid conditions such as chronic ulcers, in which the tissue shows little response, as well as conditions showing a strong tendency toward chronicity (chronic dermatitis), may be favorably influenced, according to Vogt, by an acidifying diet together with a high calcium medication.

However, we must stress at this point that there is still considerable controversy whether changes in the alkali reserve or the presence of acidosis or alkalosis are significant factors in the pathogenesis of dermatoses. Some authors claim to have demonstrated definite variations in the alkaline reserve in the blood in certain skin diseases, but others emphatically deny the occurrence of such deviations. Moreover, the opinion has been expressed that an abrupt change in the nature of the diet acts as a nonspecific stimulus leading to an alteration (*Umstimmung*) of the body's reactive capacity and that this alteration, in turn, tends to stimulate the underlying healing processes, regardless of whether the diet has an acidifying or alkalinizing effect.

The present writer feels, on the strength of his own extensive experience, that acidifying and alkalinizing diets can serve at least as valuable therapeutic adjuvants in certain dermatologic cases. An acidifying diet is indicated in some pruriginous dermatoses, ulcus cruris, and wounds showing a delay in healing. An alkalinizing diet is often beneficial in therapy-resistant urticaria and dermatitides (see p. 425).

In studying the susceptibility of animals to sensitization, considerable significance has more recently been attached to the influence of acidifying and alkalinizing diets, the former being represented by the animals' so-called "winter diet," consisting of hay, beets, and oats, the latter by their so-called "summer diet," made up of fresh grass, bran, and potatoes. The fundamental experimental work in this direcion was carried out by Sulzberger and Mayer.[150] In view of the fact that guinea pigs can very readily be sensitized to arsphenamine in winter and that in summer they can be sensitized only with great difficulty, the authors gave the animals a "winter diet" during the summer months. These animals were then found to be susceptible to sensitization. Similarly, it was demonstrated that the administration of the "summer diet" in the late fall served to counteract the seasonally high susceptibility to sensitization. The results of these experimental studies conform perfectly with Fornet's clinical observations.[151] According to Fornet, a shift in the acid-base balance leads to a change in the tuberculin reaction, individuals on an alkalinizing diet showing a weaker reaction, while those on an acidifying diet show a stronger response than previously. Moreover, von Engel[152] demonstrated that guinea pigs on a winter diet show tuberculin reactions that are stronger than those given by the same animals on a summer diet.

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[146] Schreus, H. T.: Dermat. Ztschr. **53:** 561, 1928.
[147] Marchionini, A. and Ottenstein, B.: Arch. f. Dermat. u. Syph. **163:** 61, 1931.
[148] Zitzke, E. and Peters, L.: Dermat. Wchnschr. **100:** 669, 1935.
[149] Marchionini, A.: Med. Welt **12:** 295, 1938.

However, Sandels[153] achieved entirely different results using an acidifying medicament. On the basis of Scheer's[154] encouraging work with hydrochloric acid milk in infantile dermatitis, Sandels performed a series of studies to determine the possibility of altering the skin's irritability or reactivity by giving milk prepared by adding 10 cc. of hydrochloric acid to 250 cc. of whole milk. She patch-tested 160 children for hypersensitiveness to formalin, tincture of arnica, and adhesive plaster. Fifty per cent of the children up to the age of 8 reacted to these substances. Twenty-six of the children who gave positive reactions were then put on hydrochloric acid milk, with the result that the manifestations of cutaneous susceptibility disappeared in 25 of these 26 cases.

Mom[155] obtained similar results. He experimentally produced contact dermatitis to 2,4 dinitrochlorbenzene and studied the cutaneous reaction in the presence of alkalinization with sodium bicarbonate and acidification with ammonium chloride. He found that the alkaline state favors production of experimental contact dermatitis and acidity diminishes development of the inflammatory cutaneous reaction.

How can we reconcile these diametrically opposed findings of Luithlen, Klauder and Brown, and other investigators on the one hand, and Sandels and Mom on the other regarding the influence of diet on susceptibility to sensitization? Possibly this may be explained by the fact that hydro-

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150. Sulzberger, M. B. and Mayer, R. L.: Arch. Dermat. & Syph. **24:** 537, 1931.
151. Fornet, A.: Magyar orvosi arch. **30:** 210, 1929.
152. Engel, P.: Arch. f. Dermat. u. Syph. **167:** 279, 1933.
153. Sandels, T.: Arch. f. Kinderh. **88:** 146, 1929.
154. Scheer, K.: Ztschr. f. Kinderh. **48:** 668, 1930.
155. Mom, A. M.: Rev. argent. dermatosif. **26:** 419, 1942.

chloric acid, ammonium chloride, and similar inorganic acidifiers differ in their effects on the organism from the acidifying factors of diets having an acid effect. The former are incombustible and therefore retain their full acidifying quality, while the latter, being combustible, are altered in the course of metabolism and thereby lose their acid effect to a greater or less degree. In any event, the present writer has observed, in the course of his own experimental studies in a number of patients with urticaria, that they consistently reacted with strong urticarial eruptions to various organic acids, while large doses of hydrochloric acid definitely seemed to inhibit wheal formation. Beckman[156] is also of the opinion that the more acidotic an individual is rendered, the less allergic he is likely to become.

Hoff and Spaeth[157] found that the skin's reactivity to ultraviolet and grenz rays was markedly increased in individuals on an acidifying diet (oats plus 10 Gm. of ammonium chloride daily, by mouth), and that an alkalinizing diet lowered the degree of reactivity very considerably. Schreus[158] was able to demonstrate that a normal animal eliminates more porphyrin on an acidifying diet (oats) than on an alkalinizing diet (green fodder). This difference is far more pronounced in animals subjected to experimental lead poisoning. In dealing with patients with porphyrin disease, Vannotti[159] found that an acidifying diet tended to increase porphyrin elimination and simultaneously to heighten the photosensitivity of the skin, while an alkalinizing diet had the opposite effect.

The extent to which the biologic reaction of the skin is subject to nutritional influences can be clearly and dramatically demonstrated by the effect of diet on the healing of wounds. Hippocrates recognized the fact that actual starvation or a fasting diet served to accelerate the healing of infected wounds. This important information was completely forgotten until the day when Sauerbruch,[160] quite accidentally, made similar observations on surgical patients and urged Herrmannsdorfer to investigate this question experimentally. Thereupon, Herrmannsdorfer[161] established the fact that the healing of wounds is accelerated, not only by fasting, which shifts the tissue reactions to the acid side, but also by an acidifying diet. He was able to demonstrate that when the patient is placed on such a regimen, there is generally a considerable decrease in the secretion from an infected wound. The wound begins to shrink, flabby granulations become more vigorous and bright red, and overlying pseudomembranes are speedily sloughed off. Briefly stated, the wound becomes drier and

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156. Beckman, H.: J. A. M. A. **95:** 1582, 1930.
157. Hoff, F. and Spaeth, A.: Röntgenpraxis. **1:** 600, 1929; **2:** 405, 1930.
158. Schreus, H. T. and Pouillain, H.: Arch. f. exper. Path. u. Pharmakol. **177:** 543, 1935.
159. Vannotti, A.: Porphyrine und Porphyrinkrankheiten. Berlin: Springer, 1937.
160. Sauerbruch, F.: München. med. Wchnschr. **71:** 1299, 1924.
161. Herrmannsdorfer, A.: München. med. Wchnschr. **74:** 711, 1927.

its blood supply is greatly increased. On an alkalinizing diet the granulations become quite glassy, secretion increases and often becomes foul-smelling, and the entire wound assumes a decidedly smeared appearance, with the formation of discolored pseudomembranes. The young epithelium is often sloughed off and the entire area surrounding the wound shows signs of increased edematous swelling. In short, the wound becomes increasingly moist throughout. The number of micro-organisms in the wound will decrease on an acid diet, while an alkaline diet will be accompanied by an increase in bacterial count. Similarly, independently of Sauerbruch and his co-workers, Andersen[162] described stimulation of healing processes in chronically inflamed ulcers of the skin by means of an acidifying diet. The findings reported by Sauerbruch and Andersen have been confirmed by Clairmont, Schueller, Kalk, and other observers in man, and by Vogt's studies in animals.[139] Further confirmation has been brought by the findings of Pillsbury and Sternberg.[163] These authors have reported that the manifestations of an experimental skin infection were mild in dogs that were developing an acidosis on a high fat diet, when compared with similar lesions in animals not having acidosis.

Mention might also be made here of Bonanno's studies.[164] When guinea pigs on a normal diet were given 0.2 cc of physiologic saline solution by intracutaneous injection, the fluid was absorbed in twenty-two to twenty-five minutes. This was reduced to eight to eleven minutes in animals on an acid diet, while the time in animals on an alkaline diet was the same as in normally fed animals.

An important contribution was made when Schade[165] reported on the physicochemical changes in the secretion from a wound in a dog under the influence of acidifying and alkalinizing diets. This author chose a closed wound for these experiments, since the loss of the bound carbonic acid in the exudate from an open would might disturb the acid-base balance of the tissues. The closed wound was produced by implanting small, perforated, hollow glass beads under the skin. These experiments revealed that the carbonic acid buffers underwent a marked reduction when the acid diet was used, while they showed a considerable increase when the animal was on an alkaline regimen. The outward appearance of the wound itself also exhibited contrasting changes, depending on the different forms of diet. With acidifying foods the secretion gradually subsided; on an alkaline regimen the secretion increased to such an extent that it was forced spontaneously, by its own pressure, through the puncture site in the skin. The explanation for the divergent behavior of the wound

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162. Andersen, E.: Fortschr. d. Med. **44:** 93, 1926.
163. Pillsbury, D. M. and Sternberg, T. H.: Arch. Dermat. & Syph. **35:** 893, 1937.
164. Bonanno, A. M.: Gior. di batteriol. e immunol. **20:** 687, 1938.
165. Schade, H., Beck, A. and Reimers, C.: Zentralbl. f. Chir. **57:** 1077, 1930.

secretions under the various diets was found by Schade by means of measuring the colloidal-osmotic pressure in the animal's blood. When the pH of the blood decreases, there is a rise in the colloidal-osmotic pressure in the capillaries of the wound area with a subsequent acceleration of resorption. An increase of the blood pH causes a drop in the colloidal-osmotic pressure and thus stimulates exudation.

Contrary to the findings of Herrmannsdorfer and Schade, Balint and Weiss[166] claim that a shift of the acid-base balance to the acid side increases exudation in sterile artificial inflammations as well as in ulcus cruris, whereas an alkalinizing influence tends to reduce the secretion in wounds. However, Treguboff, who reinvestigated this question, was unable to confirm Balint's findings.

Thus we are confronted with conflicting observations and views concerning the influence of diet on inflammatory processes of the skin in general. On the one hand Sauerbruch, Herrmannsdorfer, and Andersen demonstrated that an acidifying diet expedites the healing processes in inflammatory skin ulcerations. On the other hand Luithlen's experiments show that the skin is more susceptible to inflammation when the diet is acid. Lastly we have Balint's claim that an alkalinizing diet exerts a beneficial effect on ulcerative processes. All of these views are based on observations on human beings and on experimental work in animals. Which of these divergent opinions is the correct one? Kalk[167] suggests that the factor favorably influencing the healing process may be not so much the simple, relatively long-lasting effect of a shift of the acid-base balance in one direction, as the abrupt change in the pH of the skin in either direction. The present writer is also of the opinion that the action of acidifying and alkalinizing diets is to a large extent due to physico-chemical changes in the tissues and that these should therefore be properly classified as alteration diets (see p. 124). This interpretation would seem to be corroborated by the results of Hayashi's animal experiments,[137] according to which any aberration of the skin's pH from the normal, induced by a change in the diet, was followed by an increase in the susceptibility of the skin to inflammation.

Finally, Hoff[168] suggests that an acidifying diet tends, first, to intensify the inflammatory reaction by increasing the local blood supply, and that this ultimately serves to accelerate the healing process.

Methods for discovering the direction and degree of shift of the acid-base balance involve either the determination of the hydrogen-ion concentration of the blood or measurement of this alkaline reserve. The first-mentioned procedure is technically so complicated and has so many

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166. Balint, R. and Weiss, S.: Gewebsproliferation und Saurebasengleichgewicht. Berlin; Springer, 1930.
167. Kalk, H.: Klin. Wchnschr. 8: 1074, 1929.
168. Hoff, F.: Unspezifische Therapie und natürliche Abwehrvorgange. Berlin: Springer, 1930.

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possible sources of error that it is virtually of no practical value. But the alkaline reserve can readily be measured in any suitably equipped clinic or laboratory by a determination of the carbon dioxide combining power of the blood.

It is advisable to keep the patient on a mixed diet for several days before taking the blood for this test. The outcome of the examination will determine whether or not dietary therapy is to be instituted and, if so, what kind of diet is to be prescribed. A carbon dioxide combining power of 45 to 55 volumes per cent is regarded as normal, while a level below 45 volumes per cent is to be interpreted as indicating a slight acidosis. Values over 55 volumes per cent suggest a shift of the acid-base balance to the alkaline side.

To correct an alkalotic state an acidifying diet may be employed, that is, one which, after combustion, leaves a residue higher in acid than its basic radicals or, in other words, one which moves the intermediary metabolism in an acidotic direction (see Table 11).

When the examination of the blood or urine reveals a more or less pronounced acidosis, it is advisable to counteract this condition by means of an alkalinizing diet, that is to say, one which after combustion leaves a residue higher in basic than in acid radicals. Foods which may be used are included in the list shown in Table 13.

The composition of the acidifying and alkalinizing diets presented here is based largely on the comprehensive and critical evaluation of the literature by Bridges.[169]

The alterative effect (alteration, or *Umstimmung*) of dietary therapy becomes more clearly apparent when the changes in diet are introduced abruptly. The result will be more pronounced if the patient is put on an acidifying diet for three days before the therapeutic alkalinizing diet is begun, and vice versa (Marchionini[149]). In certain cases a change in the diet will soon be followed by marked improvement in the skin condition without any local treatment. Nevertheless, in most instances, some local treatment is required. Generally speaking, dietary therapy must be continued for several weeks after a clinical cure has been achieved. During this period, however, the acidifying or alkalinizing salts may be gradually discontinued. Subsequent dietary indiscretions quite commonly bring clinical recurrences. The patient may safely go back to a normal, mixed diet only after he has been free from relapses for four or five weeks.

B. DEHYDRATION DIET

A tendency to retain fluids plays an important part in the pathogenesis

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169. Bridges, M. A.: Dietetics for the Clinician. Philadelphia :Lea and Febiger, 1941.

of a number of skin diseases (Foeldes[170]). The importance of fluid retention in various conditions, including urticaria, angioneurotic edema, dermatitis, prurigo, and acne, is emphasized by the effects of an antiretentional dietary and other therapeutic measures designed to promote the excretion of fluid and sodium chloride. The question of the employment of low salt and low carbohydrate diets to this end will be discussed in detail in the following chapters. Here we shall endeavor to show that almost every component of the diet such as protein, fat, carbohydrate, and the water content of the food proper is capable of influencing the water metabolism of the skin and must, therefore, be carefully considered

TABLE 11.—*Acidifying Diet*

Purpose of the diet: To produce a shift in the pH of the tissues, including the skin, from the alkalotic to the acidotic side. The resulting decrease in the pH of the skin serves to accelerate the healing processes.

The following foods are prohibited:

Milk
Soups of all kinds
Vegetables, except fresh peas, lentils and corn
Fruits and berries, except cranberries, plums, and prunes
Sugar
Nuts, except filberts, peanuts, walnuts

The following foods are permitted:

All meats
Sweetbreads, liver, tongue, kidney, tripe, lung, heart, brain, all fresh and unsalted
Sausage
Eggs
Poultry
Fish, except smoked fish
Seafood
Game
Tea
Coffee
Fats, including unsalted butter, lard, margarine
Cheese
Rolls and bread, except pumpernickel
Noodles, spaghetti, macaroni
Oats, hominy, rice, barley, buckwheat, millet, farina, cornmeal, but not cornflakes
Corn
Lentils, fresh peas
Cranberries, plums, prunes
Nuts, except almonds, Brazil nuts, chestnuts, coconuts
Peanut butter

Administration of the following salts is recommended to augment the acidifying influence of the diet: ammonium chloride 3 Gm. (45 grains), acid sodium phosphate 3 Gm. (45 grains), or calcium chloride 2 Gm. (30 grains). Any one of these may be given three times daily.

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[170] FOELDES, E.: A New Approach to Dietetic Therapy. Boston: Badger, 1933.

in this respect in planning an antiretentional regimen. Generally speaking, it may be said that a diet high in protein or fat reduces the water content of the skin, while one rich in carbohydrates, sodium chloride, or water has the opposite effect.

TABLE 12.—*Sample Menu for the Acidifying Diet*

Type of Food	Example	Size of Portion	
		Grams	Household measure
Breakfast			
Fruit	prunes, raw or stewed	100	4 medium
Cereal	oatmeal	100	½ cup
Eggs	2 fried eggs	100	2 eggs
Bread	toasted white bread	50	2 slices
Butter		10	1 pat 1″ x 1″ x ½″
Cream	20% cream	60	2 oz.
Beverage	coffee or tea	240	1 cup
Lunch			
Fruit	prune or cranberry juice	100	½ cup
Meat, fish	filet of haddock	115	¼ cup
Vegetable	boiled rice, well buttered	100	½ cup
Bread	rye bread	25	1 slice
Butter		15	1 pat 1″ x 1″ x ¾″
Cream	20% cream	30	1 oz.
Beverage	coffee or tea	240	1 cup
Dessert	oatmeal cookies	35	3 cookies
Dinner			
Meat	lamb chops, broiled	115	¼ lb.
Vegetable	corn on cob, or canned kernels	100	1 ear 8″ or ½ cup
Bread	white flour or corn meal muffins	100	2 small muffins
Butter		10	1 pat 1″ x 1″ x ½″
Cream	20% cream	30	1 oz.
Beverage	coffee or tea	240	1 cup
Dessert	stewed or canned plums	100	2 plums

Bischoff and Voit[58] demonstrated long ago that the organs of animals raised on a preponderantly or exclusively carbohydrate diet show a higher water content than do those of animals on a diet low in carbohydrates. However, as emphasized particularly by Adlersberg and Porges,[171] all other factors (protein, salt, and acid-base balance) being equal, the tendency of a high carbohydrate diet to promote water retention becomes

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171. ADLERSBERG, D. and PORGES, O.: Klin. Wchnschr. **12:** 1446, 1933.

apparent only when viewed in comparison with the influence of a dietary high in fat. In other words, a high carbohydrate, low fat diet makes for water retention. Yet a diet rich in carbohydrate but poor in sodium definitely exerts a dehydrating influence (von Noorden[172]). Similarly, a dietary extremely poor quantitatively in protein promotes dehydration, even in the presence of maximal amounts of carbohydrates. The salient point in Adlersberg's observations is that storage of the water retained on a high carbohydrate diet takes place notably in the skin. This fact was disclosed by the observation that there was a shortening of the resorption time of intracutaneously injected saline solution. It is well known that the higher the water content of the skin, the more rapid the disappearance of a wheal produced by an intracutaneous injection. Haldi, Giddings, and Wynn[173] showed experimentally that in the albino rat the percentage

TABLE 13.—*Alkalinizing Diet*

Purpose of the diet: To produce a shift in the pH of the tissues, including the skin, from the acidotic to the alkalotic side. It is of value in the treatment of skin diseases where the tissues show a definite tendency to the acidotic side.

The following foods are prohibited:

All meats
Sweetbreads, liver, tongue, kidney, heart, brain, lung, tripe
Sausage
Eggs
Poultry
Fish
Seafood
Game
All fats and oils, including butter, margarine, lard
Cheese
Rolls and bread, except pumpernickel
Noodles, spaghetti, marcaroni
Cereal grains and prepared cereals except corn flakes
Corn, lentils
Cranberries, plums, prunes
Nuts, except almonds, Brazil nuts, chestnuts, coconuts

The following foods are permitted:

Milk
Pumpernickel and soya flour products
All vegetables except corn, lentils, and fresh peas
All fruits except prunes, plums, and cranberries
Nuts, except almonds, Brazil nuts, chestnuts, coconuts
Marmalade, jellies, jam, preserves
Coffee, tea, cocoa

In support of this diet one may prescribe 0.5 Gm. of sodium bicarbonate three times daily.

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[172] von Noorden, C.: Alte und neuzeitliche Ernährungsfragen. Vienna: Springer, 1931.

[173] Haldi, J., Giddings, G., and Wynn, W.: Am. J. Physiol. **135:** 392, 1942.

of water of the skin is appreciably lower on a high fat than on a high carbohydrate ration. The diet may affect the amount of water of the skin by increasing or decreasing the fat deposition in this tissue, since there is an inverse relationship between the water and fat content of the cutis and the subcutaneous tissue.

There is generally an increase in the water content of the skin when the diet is insufficient, as seen in cases of famine edema. This can probably be explained by the relative lack of protein in certain essential amino acids and also by the preponderance of carbohydrate in the diet. Stokes and associates[174] are of the opinion that the dehydrating action of a high protein diet is attributable to its acid-ash properties.

TABLE 14.—*Sample Menu for the Alkalinizing Diet*

Type of Food	Example	Size of Portion	
		Grams	Househould Measure
Breakfast			
Fruit	orange juice	120 cc.	½ cup
Cereal	corn flakes	30 Gm.	⅓ cup
Milk	whole milk	360 cc.	1½ cups
Bread	pumpernickel	25 Gm.	1 slice
Beverage	cocoa, all milk	240 cc.	1 cup
Lunch			
Fruit	apricot juice	120 cc.	½ cup
Vegetables	Vegetable platter of spinach, carrots, boiled potato, stewed tomato; quantity of each	100 Gm.	½ cup
Bread	soya bread or soya crackers	25 Gm.	1 slice
Beverage	coffee with milk 3 oz.	240 cc.	1 cup
Dessert	sliced peaches, fresh or canned	140 Gm.	½ cup
Dinner			
Soup	vegetables, cooked in milk	250 cc.	1 cup
Vegetables	vegetable platter of boiled onions, fried potatoes, squash, boiled cabbage with white sauce of soya flour, quantity of each	100 Gm.	½ cup
Bread	pumpernickel	25 Gm.	1 slice
Beverage	tea	240 cc.	1 cup
Dessert	baked apple	120 Gm.	medium size

Sakata[60] demonstrated that the quantity of water in the skin depends on whether the animal is given moist or dry food. The skin of rabbits on a moist ration showed an average water content of 72 per cent, as compared with the corresponding figure of 62.7 per cent for animals on dry fodder. Fasting, both with and without water, appreciably reduces the water content of the skin (Koenigstein[61]). Moreover, fasting and low liquid diets are known to combat inflammation and promote healing (Nathan and Stern[175]). Water, given by mouth, increases the water content of the blood and skin of animals. However, in fasting animals, this increase is far greater in the skin than in the blood (Toshima[176]).

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[174] STOKES, J. H., BEERMAN, H., and INGRAHAM, N. R., JR.: Am. J. M. Sc. 195: 562, 1938.

Pillsbury and Kulchar[177] presented experimental evidence that in rabbits a gross disturbance in the water balance has a profound influence on the course of an experimental infection. Dehydrated rabbits will withstand an infection of the skin as well as or even better than those on a normal fluid intake; and a quiescent infection may at times flare up when the water intake is increased (Kulchar and Alderson[178]).

TABLE 15.—*Anti-retentional Diet*

Purpose of the diet: To dehydrate the skin in inflammatory dermatoses and those with fluid retention.

The following foods are prohibited:

Pork
Sausages
Turkey, duck, goose
Salmon, mackerel, herring, carp, fish roe
Cheese, except plain cottage cheese
Fats, including butter, lard, vegetable shortenings, margarine
Salt to be used sparingly and only in preparing food
Water limited to 750 cc. per 24 hours

The following foods are permitted:

Lean beef
Liver, sweetbreads, kidney, tripe, lung
Chicken
Eggs
Fish, unsmoked, fresh (except salmon, mackerel, herring, carp, fish roe)
Oysters
Gelatin
Milk
Cream
Cottage cheese, plain
Bread
Cereals
Macaroni
All vegetables
All fruits
Nuts
Salad oils in limited amounts

Antiretentional therapy is therefore indicated in dermatoses with fluid retention and possibly also in acute bacterial cutaneous infections. Foeldes[170] and Barber[179] stress the great value of this form of diet in seborrheic

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175. Nathan, E. and Stern, F.: Dermat. Ztschr. **60:** 299, 1931.
176. Toshima, E.: J. Kumamoto M. Soc. **13:** 2264, 1937.
177. Pillsbury, D. M. and Kulchar, G. V.: Am. J. M. Sc. **190:** 169, 1935.
178. Kulchar, G. V. and Alderson, H. E.: Brit. J. Dermat. **48:** 477, 1936.
179. Barber, H. W.: Practitioner **142:** 1, 1939.

conditions. It may be interesting to note that both authors point to the great reduction of frequency and intensity of colds and asthmatic attacks under this regimen. Stokes et al.[174] raise the question whether the recrudescence of premenstrual acne may not be due to the accumulation of water in the tissues at that period of the cycle, consequently influencing inflammatory manifestations in the skin. The favorable effect of dehydrating measures, such as large doses of ammonium chloride, may be cited in this connection. An antiretentional diet should contain a relatively high proportion of proteins and nucleoproteins, with limited quantities of carbohydrates and fats. Green vegetables and fruit of all kinds may be given freely. Needless to say, the fluid intake and the consumption of NaCl must be restricted.

TABLE 16.—*Sample Menu for the Anti-retentional Diet*

Type of Food	Example	Size of Portion	
		Grams	Household measure
Breakfast			
Fruit	grapefruit	100	½ medium size
Cereal	oatmeal	40	½ cup
	with cream	60	¼ cup
Egg	2 eggs		
Bread		50	2 slices
Beverage	milk	100	2/5 cup
Lunch			
Meat	broiled liver	115	¼ lb.
Vegetables	macaroni, stewed tomatoes, sliced beets, broccoli; quantity of each	120	½ cup
Bread		25	1 slice
Beverage	⅔ coffee, ⅓ milk	100	2/5 cup
Dessert	mixed fruit cup of grapes, diced apple, frosted strawberries	125	1 cup
Dinner			
Meat	lean roast beef	115	¼ lb.
Vegetables	string beans	75	¾ cup
	brussels sprouts	100	½ cup
Salad	lettuce	50	2 large leaves
	shredded carrot	50	⅓ cup
	cottage cheese	55	¼ cup
Bread		50	2 slices
Beverage	tea	100	⅓ cup
Dessert	canned pears	125	2 halves

Barber[179] believes that the diuretic effect of a high protein diet is in part due to urea, whose diuretic properties are well known. Moreover, the nucleoproteins contain purin bases which are chemically closely related to the xanthine group of diuretics.

In addition to the antiretentional dietary, diuretics may temporarily be used with advantage. Foeldes[170] advises calcium carbonate (3 Gm. three times daily) or, if there is achlorhydria, calcium lactate (3 Gm. three times daily). Barber[179] gives large doses of potassium citrate (1 Gm. four times daily) if there is urinary hyperacidity as indicated by the pH of the urine.

C. LOW SODIUM CHLORIDE DIET

Restriction of table salt intake is a dietary measure that can be of value in many ways, notably in the treatment of certain dermatoses. The effects of a diet composed of unsalted nutrients—in brief, a low salt diet—can be enhanced by giving preference to foods poor in Na and Cl. Since aliments do not contain equal quantities of sodium and of chloride one must not make the common error of referring to the sodium chloride content in a given aliment instead of its chloride and its sodium.

To understand this postulate, it should be remembered that one cannot properly speak of a sodium chloride or salt metabolism, for this would imply that the ratio between sodium and chloride in the body is always constant, as in NaCl. Such is by no means the case, as countless pharmacologic studies have shown. In the organism the quantity of sodium is generally balanced very precisely against the sum of the quantities of chloride and bicarbonate (Heubner). We must assume, therefore, that the metabolism of sodium and that of chloride are at least partially independent, and we must consequently reckon with this possibility with regard to their excretion in the urine as well.

Even if the sodium and chloride are generally administered simultaneously in the form of table salt in food, their respective ions are known to have different functions to perform in the organism Thus, sodium is closely connected with the water balance; furthermore, as a base it plays a part in regulating the acid-base balance. The performance of every individual cell is determined by the Na:K:Ca ratio. Chloride, on the other hand, is essential to normal gastric digestion and to respiration. Sodium chloride itself is the very basis of osmotic regulation in the organism.

Doellken[180] determined that, after four or five days of low salt diet, constant quantities of chlorides and sodium (approximately 2 Gm.) are excreted in the urine. However, the chlorides and sodium are not eliminated in amounts corresponding to their ratio in table salt; the quantity of sodium eliminated is smaller than would be expected. Thus, a part of the ingested sodium does not leave the organism as NaCl, but is retained in the body or excreted otherwise than in the urine. On a strictly salt-free diet—that is, when no salt is added whatsoever and when every effort is made to select aliments which are, in themselves, salt-poor (e.g., fruit and fruit juice diets)—the quantity of sodium and chloride eliminated in the urine in twenty-four hours does not exceed 0.8 to 1 Gm.

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[180] Doellken, H.: Arch. f. Dermat. u. Syph. 175: 515, 1937.

The therapeutic effectiveness of sodium chloride restriction in the skin diseases is attributable to a tendency on the part of such a dietary to promote dehydration and reduce susceptibility to inflammation. It is now generally assumed that the reduction in sodium intake resulting from a salt-poor diet plays the chief role in promoting dehydration. Furthermore, the susceptibility to inflammation is believed to be reduced by the relative increase in the calcium content of the tissues, as a result of a relatively reduced NaCl intake (Luithlen).

These two noteworthy properties of a low salt diet explain the gratifying results obtained, particularly in acute inflammatory skin diseases as well as in skin conditions associated with edema. These diseases include, above all, acute dermatitides, erythrodermias, contact dermatitis with edema, dermatoses of the lower extremities due to venous stasis, urticaria, and certain forms of pruritus. However, most authors reporting their experience with this form of diet invariably mention that this approach has met with only partial success, some cases responding very satisfactorily while others remained apparently unchanged.

Low salt diets in the form of what are known as the Gerson diet and the Sauerbruch-Herrmannsdorfer diet have been found to be especially valuable in certain forms of skin tuberculosis, notably lupus. These diets (which will be discussed in detail on p. 65) are not only poor in salt but also in carbohydrates and relatively restricted in protein, while their vitamin and mineral contents are high. Bommer[181] has presented histologic evidence demonstrating that the first effect of a low salt diet is seen in its influence on the vascular system. The edema and venous stasis which characterize inflammatory lesions are reduced, and thus the normal function of cells of the walls of the blood vessels in the inflamed area is restored. Bommer's microscopc studies of the capillaries in the lesions of lupus revealed, furthermore, that dietary therapy serves to improve the impaired distribution of blood in the affected area, as shown by the fact that the blood vessels reassume their bright red color and the vessels which make up the superficial cutaneous plexuses become less distended. The same author observed similar changes following this dietary treatment in cases of skin damage caused by roentgen rays. Hval[182] found that the difference between the number of capillaries in the tuberculous

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181. Bommer, S.: Am. Rev. Tuberc. **27:** 209, 1933.
182. Hval, E.: Acta dermat.-venereol. **13:** 593, 1932.

skin of a patient on a Sauerbruch-Herrmannsdorfer diet and those in a patient not on this diet was so great that, in the former, the circulation in a given area might well have been doubled. This may explain why skin tuberculosis in particular is so favorably affected by the diet. Scolari's[183] electrothermic studies and microscopic investigations of the capillaries reveal that, far more commonly than can be observed on mere clinical inspection, initiation of dietary treatment is followed by signs of increased circulatory activity in the lupus foci (hyperemia and formation of new vessels).

On the other hand, a low salt diet may increase the sensitivity of the skin. Thus, Koenigstein[184] was able to demonstrate that the reactions of animals on a salt-poor diet to various kinds of irritation to the skin and mucous membranes (for example, intracutaneously injected diphtheria toxin, mustard oil applied to the conjunctiva) are considerably stronger than the reactions of animals on a high salt diet. The intensity of the reactions can be further increased by drugs which remove sodium chloride from the organism. Kile and Pepple[185] demonstrated that allergic reactions were stronger in sensitized animals on a salt-free diet than in the controls. Gerson[15] observed that on the low salt diet which bears his name, tuberculous patients manifested a definite rise in sensitivity to irradiation therapy and to tuberculin, as well as to chemical irritants. Engelhardt,[186] Popper,[187] Doerffel,[71] and other authors were able to confirm these observations. Moreover, administration of table salt brings about a considerable reduction in the irritability of the skin.

The importance of sodium chloride in the biologic reactivity of the skin is further demonstrated by the influence of a high salt intake. By means of the so-called sodium thrust it was shown by Keining and Hopf[81] and confirmed by Eller and associates[188] that a high salt diet tends to exacerbate skin manifestations and pruritus. Ballestero and Mom[189] studied cases of experimental contact dermatitis produced by 2,4,dinitrochlorbenzene in a group of patients receiving increased quantities of salt and in a second group whose salt intake was decreased. The patients receiving larger amounts of salt reacted to the chemical irritant both subjectively and objectively more quickly, with greater intensity and for a longer time. An evident effect was produced also on previously existing dermatoses. Contrariwise, diets with decreased quantities of salt favorably influenced the course of experimental dermatitis and pre-existing dermatoses. These

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183. Scolari, E.: Giorn. ital. di dermat. e sif. **76:** 665, 1935.
184. Koenigstein, H.: Wien. med. Wchnschr. **83:** 842, 1933.
185. Kile, R. L. and Pepple, A.: J. Invest. Dermat. **1:** 59, 1938.
186. Engelhardt, W.: Dermat. Wchnschr. **90:** 72, 1930.
187. Popper, M.: Strahlentherapie **45:** 235, 1932.
188. Eller, J. J. and Rein, C. R.: New York State J. Med. **32:** 1296, 1932.
189. Ballestero, L. H. and Mom, A.: Rev. argent. dermatosif. **26:** 1115, 1942.

experiments indicate that sodium chloride encourages cutaneous inflammation, while diets with reduced amounts of sodium chloride considerably reduce the reactivity of the skin.

A low salt diet can be planned in a number of ways. The choice lies, fundamentally, between a low salt diet composed of aliments to which no salt is added for flavoring or cooking purposes, and a strictly salt-free diet consisting exclusively of foods which in themselves contain minimal quantities of sodium (Table 17) and chloride (Table 107). The former category includes the Gerson diet, the Sauerbruch-Herrmannsdorfer diet, and the raw food diet and restricts the daily intake of sodium chloride to 2.5 to 4.0 Gm. If the food is skillfully prepared this form of diet can easily be continued for some time. Dishes may be made more palatable by adding lemon, onion, caraway, anise, parsley, dill, poppyseed. Virtually salt-free dietary regimens, in the form of milk, fruit, or fruit juice diets, can hardly be continued for more than two or three consecutive days.

TABLE 17.—*Sodium Content of Various Foods*

Foods Highest in Sodium		*Foods Lowest in Sodium*	
Bread	Egg white	Cereals	Fruits
Biscuits	Cheese	Flour	Fruit juices
Crackers	Carrots	Macaroni	Kidney beans
Wheat bran	Endive	Wheat gluten	Lettuce
Wheat germ	Lima beans, dried	Meat	Parsnips
Caviar	Olives	Cream	Potatoes
Oysters	Spinach	Honey	Squash
Clams	Water cress	Molasses	Tomatoes
Meat extract	Raisins	Maple syrup	Chocolate
	Paprika		
	Pepper, black		
All foods treated by pickling, brining, corning, smoking, or salting			

1. MILK DIET

Dardel[190] seems to have been the first to recommend a strict milk diet for treating acute inflammatory conditions of the skin. He prescribed 500 cc. of milk, mixed with Vichy or lime water, every three hours. If the milk caused constipation, bacillus acidophilus milk was given instead. When the acute condition had subsided, the patient was put on a milk and vegetable regimen. This dietary method was apparently completely forgotten until Meyer[191] called attention to its usefulness in acute derma-

[190] DARDEL: J. des Pract. No. 7, p. 106, 1912; No. 8, p. 121, 1912.

[191] MEYER, J.: J. des Pract. No. 47, p. 769, 1925; No. 48, p. 790, 1925; No. 49, p. 806, 1925.

titis. Meyer demonstrated that a healthy person loses only some 1,200 Gm. in weight on a diet of approximately 2 liters of milk in forty-eight hours. However, a patient with acute dermatitis loses from 1,500 to 4,000 Gm. and, at the same time, the skin condition almost invariably shows marked improvement. Subsequently, however, Meyer[70] modified the method somewhat and prescribed 1 liter of milk plus 1 liter of Vichy water (or distilled water when Vichy is not available) daily for two or three days. The patient is confined to his home during this period. Thereafter he is put on a low salt diet for one or two weeks, to prevent a resumption of water retention, while at the same time the intake of fluid is restricted. Beginning on the fourth day of the low salt diet, Meyer gives 0.10 Gm. desiccated thyroid for four consecutive days to maintain the diuresis.

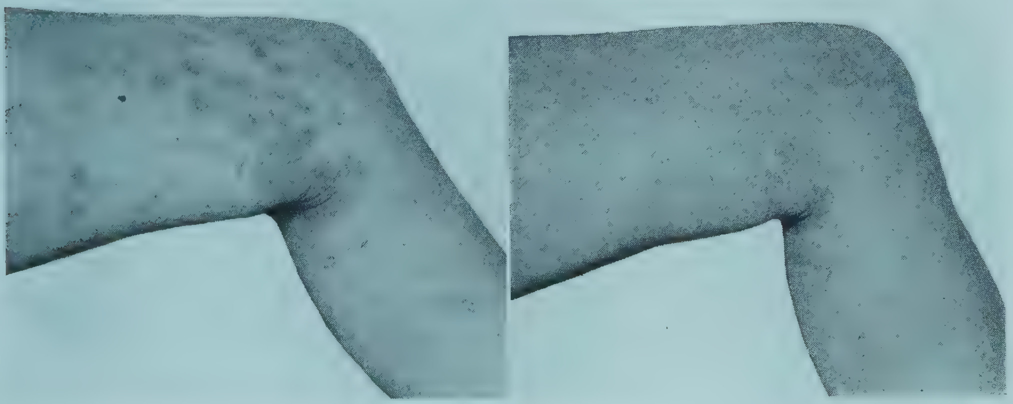

FIG. 1 FIG. 2

EFFECT OF MILK DIET ON ACUTE DERMATITIS

FIG. 1. Appearance of dermatitis before treatment.

FIG. 2. After two days of a diet consisting of one liter of milk plus one liter of distilled water.

Meyer compared various forms of diets from the viewpoint of their dehydrating effects in dermatitis patients. Complete abstinence from food and drink ("absolute diet") does not cause a marked loss in weight but soon leads to anuria and cannot therefore be continued for any length of time. A "water diet" which consists only of 2 liters of water a day leads to moderate diuresis and to an appreciable loss in weight; however, since this diet is very debilitating it cannot be maintained for more than one or two days. As noted above, the "milk diet," on the other hand, has proved to be satisfactory with regard to maintainence of diuresis without serious loss of body weight.

The beneficial action of the Dardel-Meyer milk dietary in acute inflammatory dermatoses (Figs. 1 and 2) is attributable mostly to dehydration and to a decrease in the sodium chloride content of the skin. This is in accord with the results of chemical studies of the skin by the present writer[10] and by Chiale,[192] which showed that the water and sodium chloride content of the skin are abnormally high in the acute stages of dermatoses such as dermatitis, erythroderma, and psoriasis (see p. 20).

There can be no doubt that a milk diet exerts a chemical as well as a physicochemical influence on the organism, particularly on the skin. However, the writer is of the opinion that the greatest virtue of all these diets lies in the fact that they produce an abrupt metabolic change, thus creating an *ictus therapeuticus* which cannot be achieved in any other manner. This question will receive further attention below, when alteration diets are discussed (p. 124).

2. Fruit and Fruit Juice Diets

The indications for a fruit diet and a milk diet are about the same. On the first day the patient is given 1 Kg. of any kind of fresh fruit plus 750 cc. of fruit juice. On the second day vegetables, prepared without salt, are added. If the patient does not tolerate fruit juice or if it is not available, 1½ to 2 Kg. of raw apples or oranges may be given for one or two days.

This diet, being practically salt-free, has a stronger diuretic effect than the milk diet and therefore more actively promotes the elimination of salt. This is illustrated by the following observation: When a low salt diet is given for four or five consecutive days, the sodium and chloride begin to be eliminated in constant daily quantities. If the patient is then put on a fruit diet for one or two days there is, as Doellken[193] has shown, a pronounced increase in diuresis; in other words, dehydration is intensified.

3. Raw Food Diet

The raw food diet was introduced by Bircher-Brenner as early as 1895. He describes it as a diet composed exclusively or predominantly of edible plant life (fruits, leaves, roots, nuts, seeds) in an uncooked condition, with meat, egg, cheese, white flour, sugar, sodium chloride, and alcohol strictly excluded. This diet is rich in potassium and poor in sodium. Since potassium has a diuretic effect, and since a sodium-poor diet acts more or less in the same manner, this regimen promotes the excretion of the abnormal quantities of water and of sodium chloride retained, notably, in acute inflammatory dermatoses. However, it seems doubtful that the excellent results obtained with the raw food diet can be attributed exclusively to the extremely unequal ion administration which leads to replacement in the skin of one ion by another (transmineralization) on a considerable scale. In all probability the abruptness of the dietary change plays a significant role, exerting an influence that can best be described by the concept of alteration therapy (p. 124). However, this diet should not be continued for more than five or six weeks. Its success depends largely on the skill with which the dishes are prepared. Salads, vegetables, vegetable cocktails, fruits, and fruit juice cocktails offer abundant possibilities to the creative imagination of the culinary expert (Holbrook[194]).

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[192] Chiale, G. F.: Giorn. ital. di dermat. e sif. 75: 1615, 1934; 76; 703, 1935.

[193] Doellken, H.: Deutsche med. Wchnschr. 62: 1004, 1936.

The principal difference between the strictly vegetarian and the raw food diets is that the former admits of considerable cooking. The Sauerbruch-Herrmannsdorfer diet, like the raw food diet, rules out table salt and salty foods and gives preference to raw fruits and vegatables; but the former does not prohibit cooked foods and it allows 1.5 liters of milk daily and 500 Gm. of meat per week.

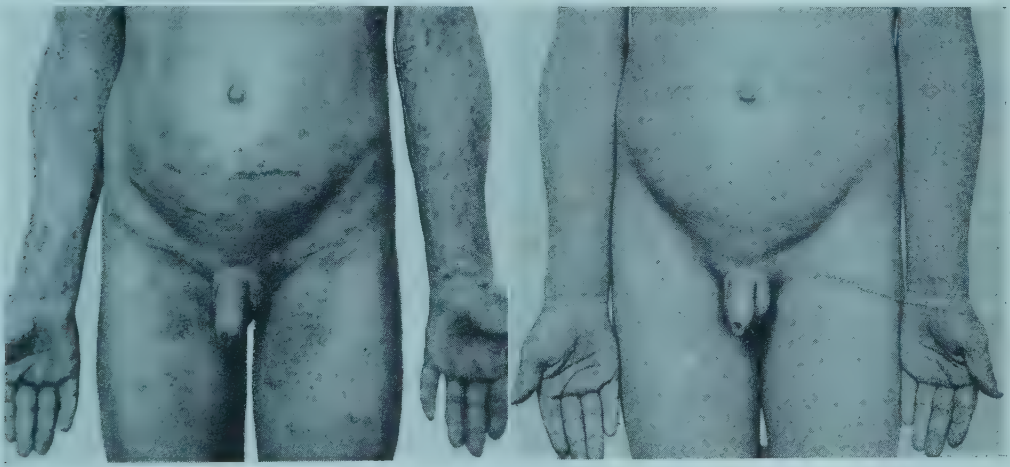

Fig. 3 Fig. 4

Effect of Raw Food Diet on Neurodermatitis in an 8 Year Old Boy

Fig. 3. Appearance before treatment.

Fig. 4. After two weeks of strict raw food diet.

The writer has often obtained highly gratifying results with the raw food diet in severe cases of refractory chronic dermatitis as well as neurodermatitis (Figs. 3 and 4) and in arsphenamine dermatitis, chronic urticaria, and pruriginous dermatoses. Moreover, this diet has a strongly anti-inflammatory action. Bommer[195] rightly points out, however, that this kind of diet is capable of producing hypersensitivity to sunlight, notably in the spring. Under certain circumstances this may, of course, cause exacerbation of a given skin disease.

4. Gerson and Sauerbruch-Herrmannsdorfer Diets

The literature contains frequent references to the Gerson-Sauerbruch-Herrmannsdorfer diet. This is probably due to the fact that Gerson and

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[194] Holbrook, A. A.: Ann. Int. Med. **20:** 512, 1944.

[195] Bommer, S.: Deutsche med. Wchnschr. **64:** 1644, 1938.

Sauerbruch worked together in the latter's clinic for some time, studying dietary therapy in bone and skin tuberculosis, and then jointly published their findings. Actually, however, the Gerson diet and the Sauerbruch-Herrmannsdorfer diet are by no means identical, although they achieve similar results in tuberculosis and in other chronic diseases. This is in all likelihood due to the salt restriction which is common to both diets and which leads to marked dehydration of the tissues and to a modification of the organism's mineral balance. Thus, Blumenthal and Funk[196] reported that reddening and swelling of lupus foci reappeared when salt (3 Gm. sodium chloride three times daily) was given for a few days, while the healing tendency was resumed, in most cases, just as soon as the salt intake was again rigorously restricted.

TABLE 18.—*Chief Differences between the Gerson and the Sauerbruch-Herrmannsdorfer Diets*[197]

	Gerson Diet	Sauerbruch-Herrmannsdorfer Diet
Meat	At most 100 Gm. once a week	500 Gm. per week
Viscera	Prohibited	Permits spleen, liver, sweetbread, brain, lung, kidney
Fish	Only about 70 Gm. per week	Permitted
Milk	250 cc. daily	1,250 cc. daily
Protein	Daily average about 40 Gm.	Daily average about 90 Gm.
Fat	Moderate amounts	160–200 Gm. daily
Cream	Prohibited	About 250 cc. daily
Carbohydrate	Generous amounts	About 200–240 Gm. daily
Potatoes	Generous amounts	Not more than 125 Gm. daily
Egg	Only yolk of eggs	Whole eggs
Raw food	Predominant constituent of diet: 1,500–2,000 cc. of raw fruit juices and raw vegetable juices daily	Subordinate constituent of diet: 100 Gm. raw vegetables and 375 Gm. raw fruit daily

Herrmannsdorfer's assumption that the efficacy of his diet was attributable solely to its acidifying action[161] was rejected by other authorities, including von Noorden and Kroetz. Moreover, many observers believe that the effectiveness of both the Gerson and the Sauerbruch-Herrmannsdorfer diets is due in great part to the abrupt and drastic dietary change, i.e., to the action of what is known as alteration therapy (p. 124).

Before presenting the two dietaries in detail, it may be useful to study a tabulation of the differences between them.

The Gerson diet may be summarized as being predominantly vegetarian,

[196] BLUMENTHAL, F. and FUNK, C. F.: Strahlentherapie **45:** 49, 1932.

[197] HERRMANNSDORFER, A. and HERRMANNSDORFER, M.: Kochbuch für Tuberkulöse. Leipzig: Barth, 1931.

alkalinizing, low in protein and in carbohydrates, high in fats and in vitamins, with table salt almost totally excluded. The Sauerbruch-Herrmannsdorfer diet is a mixed diet, probably acidifying, moderately high in fat, decidedly low in carbohydrates, rich in vitamins, with table salt practically excluded. Both diets lay great stress on uncooked aliments of vegetable and animal origin, such as raw fruits and vegetables, uncooked eggs, raw milk, and raw chopped meat. In addition to calling for a preponderance of raw foods these dietaries specify that such foods as are cooked should be roasted, broiled, boiled, or baked for as short a time as possible and the prepared dishes be eaten promptly to avoid the necessity of rewarming them.

At first glance, therefore, the Gerson diet and the Sauerbruch-Herrmannsdorfer diet appear to be very much alike, but on closer inspection they are found to differ considerably. Almost all of the reported favorable results were achieved with the Sauerbruch-Herrmannsdorfer diet because it is easier to prepare and more palatable then the Gerson diet.

It is advisable to hospitalize the patient during the course of the Gerson diet as well as the Sauerbruch-Herrmannsdorfer diet, at least in the beginning, largely for the purpose of acquainting him with the aims of the therapeutic measures. Furthermore, this should serve to give the patient a practical understanding of the more important details of the procedure. Last but not least, this will help to overcome his aversion to a low salt diet by giving him an opportunity to see the beneficial effects of the treatment in patients who have been on such a diet for some time. It must be emphasized that nothing like a permanent result can be achieved by means of the low salt diet unless the patient is able and willing to adhere strictly to it and to continue doing so for many months. After discharge from the hospital, however, this depends not only on the patient's will power and desire to get well, but also on the manner in which the food is prepared and presented. A number of helpful culinary guides are available for this purpose, including, notably, Herrmannsdorfer's book.[197]

5. Equilibrated Salt (Titro Salt) Therapy

Generally speaking, patients find any type of low salt diet extremely distasteful. Both the Gerson and the Sauerbruch-Herrmannsdorfer diets are rather complicated, relatively expensive, and usually require hospitalization of the patient. Moreover, the ordinary salt substitutes are, as a rule, disappointing.

Keining and Hopf[81] have recently attempted a new approach to the entire problem. It is now generally assumed that the action of sodium chloride which causes exacerbation of cutaneous symptoms is due to sodium

TABLE 19.—*Gerson Diet*[198]

Purpose of the diet: Alteration of metabolism by means of a dietary low in sodium chloride but high in other mineral salts and in vitamins.

The following foods are prohibited:

- Table salt in cooking and at the table
- Soups
- Canned foods
- Pepper, mustard, vinegar, spices
- Salted and smoked meats of all kinds
- Salted and smoked fish, caviar, sardines
- Salted bread, cake, pastry
- Chocolate and cocoa
- Salted cheese
- Sugar (up to 20 Gm. or ⅔ oz. per week is permitted)
- Honey (up to 60 Gm. or 2 oz. per week is permitted)
- Cream, except as occasional addition to foods, ice cream and other similar dishes
- Alcohol (except vermouth, Malaga wine, cognac as prescribed)
- Tobacco (even a single cigarette is prohibited)
- Coffee and tea
- Carbonated waters, mineral waters, bottled lemonades

The following foods are permitted:

	Daily allowance
Fresh milk	200 Gm. (6 oz.)
Cream	10 Gm. (⅓ oz.)
Cream cheese and unsalted limburger	20 Gm. (⅔ oz.)
Butter, unsalted	100 Gm. (3 oz.)
Bread, salt-free	60 Gm. (2 oz.)
Potatoes	300 Gm. (10 oz.)
Oatmeal	40 Gm. (1⅓ oz.)
Oil	25 Gm. (1 oz.)
Vegetables	500 Gm. (16 oz.)
Fruits	500 Gm. (16 oz.)
Yolk of egg, raw	4 yolks
Vegetable juice made as follows: ⅔ from spinach, carrots, beets; ⅓ from oyster plant, kohlrabi, tomatoes, celery, leeks	1,400 cc. (3 pints)
Fruit juice prepared from lemons, oranges, grapes, or apples	600 cc. (18 oz.)

	Additional weeky allowance
Cream	150 Gm. (5 oz.)
Egg, whole	1 egg
Sugar	20 Gm. (⅔ oz.)
Honey	50 Gm. (2 oz.)
Farina	50 Gm. (2 oz.)
Meat	100 Gm. (3 oz.)
Fish	70 Gm. (2 oz.)
Wheat flour	35 Gm. (1 oz.)
Rice	50 Gm. (2 oz.)
Almonds	00 Gm. (3 oz.)
Other nuts	100 Gm. (3 oz.)
Plums	200 Gm. (6 oz.)

In order to make the food palatable one may use liberal amounts of the following flavoring adjuvants: marjoram, tarragon, dill, onion, peppermint, bay leaves, chives, caraway seeds, parsley, celery, garlic, soup greens (pot herbs), vanilla, ginger, cinnamon, anise, currants, almonds, coconut, nuts, raisins, leeks. One may also add to the dishes lemon, horse-radish, radishes, olive oil, Malaga wine, red wines, homemade fruit juices. Some meat extract is also permitted.

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[198] GERSON, M.: Münch. med. Wchnschr. 77: 967, 1930.

which disturbs the equilibrium between itself and the other cations in the organism (see p. 26). With this in mind, Keining and Hopf conceived the idea of equilibrating the minerals in the same proportion as they are found in the blood plasma and in sea water. Their formula for such a salt mixture, which they termed Titro Dietetic Salt (also known as Toti Balanced Salt),* is as follows:

Table 20.—*Sample Menu for the Gerson Diet*

Breakfast
Vegetable or fruit juice; unstrained oatmeal gruel with butter

Mid-morning
2 or 3 raw egg yolks with lemon; grated radish, tomato or fruit; 30 Gm. (1 oz.) of cottage cheese

Lunch
Vegetable pudding with horse-radish sauce; steamed beets; mashed potatoes; salad with grated carrots; caramel cream; salt-free bread heavily buttered

Mid-afternoon
250 cc. (8 oz.) fresh milk

Dinner
Steamed tomatoes; rice; lettuce; fruit; salt-free bread heavily buttered

Before retiring
Oatmeal gruel with butter

Taken throughout the day: Fruit or vegetable juices

The caloric intake is made up as follows:

Proteins:	67 Gm. equivalent to	275 calories or 10% of total calories
Fats:	170 Gm. equivalent to	1,581 calories or 56% of total calories
Carbohydrates:	235 Gm. equivalent to	964 calories or 34% of total calories

Thus the patient theoretically receives 2,820 calories and about 2 Gm. of sodium chloride a day, a quantity sufficient to maintain the secretion of hydrochloric acid in the stomach.

Sodium	32.51%	Chloride	52.63%
Calcium	1.42%	Lactate	3.79%
Magnesium	0.86%	Citrate	0.5%
Potassium	2.7%		

Keining and Hopf[81] as well as Eller and Rein[188] demonstrated marked exacerbations of symptoms in chronic dermatitis, urticaria, lichen planus, lupus vulgaris, and acne after flooding the organism with sodium chloride.

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* Nordmark Chemical Works, Inc., New York, N. Y.

These cases showed improvement, however, on a diet which was free from table salt, but in which equilibrated salt was used.

Bommer[199] reported that his results with the equilibrated salt diet in 33 cases of lupus vulgaris were fully as favorable as those obtained with the low salt Sauerbruch-Herrmannsdorfer diet. Langer[200] and Schubert[201] confirmed Keining's findings, particularly with regard to dermatitides.

TABLE 21.—*Sauerbruch-Herrmannsdorfer Diet*[197]

Purpose of the diet: Identical with that of the Gerson diet (p. 68).

The following foods are prohibited:

Table salt
Canned foods
Smoked or spiced meats of all kinds
Bouillon cubes, meat extracts except as listed under permitted foods
Salted butter
Ordinary bread
Soda crackers or other salted crackers
Cheese, except homemade cottage cheese or commercial salt-free cheese
Shrimps
Smoked or pickled fish
Alcohol, except wine for flavoring purposes
Water as a beverage

The following foods are permitted:

Flour, about 30 Gm. (1 oz.) daily
Unsalted bread, about 60 Gm. (2 oz.) daily: corn bread, pumpernickel, or zwieback, about 20 Gm. (⅔ oz.) daily
Noodles, macaroni, spaghetti
Potatoes, not more than 125 Gm. (4 oz.) daily
Sugar, about 30 Gm. (1 oz.) daily; brown sugar and honey may also be used
Rice, farina, tapioca, barley, oatmeal
Fresh meat, about 500 Gm. (16 oz.) weekly
Viscera such as sweetbread, calf's brain, liver, lung, kidney, spleen
Fresh fish
Milk, about 1,000 to 1,500 cc. (2 to 3 pints), in any form but especially fresh milk
Fats, about 80 to 100 Gm. (3 oz.) ununsalted butter, olive oil, lard, or unsalted bacon daily
Fruit, as much as possible of fresh fruit, but also stewed and preserved fruits, dates, figs, raisins, nuts, marmalades, jams, jellies, compotes, milk of almonds, fruit cake
Vegetables, large amounts of fresh vegetables of all kinds, steamed, not boiled. Also unsalted sauerkraut, lettuce, cucumber, endive, watercress
Eggs as such and also in sauces, puddings, porridge, and creams
Spices and herbs: marjoram, tarragon, dill, peppermint, chervil, onions, capers, bay leaves, juniper, chives, caraway seeds, lemons, parsley, sage, rosemary, celery, garlic, horse-radish, radish, soup greens, ginger, cinnamon, anise, and currants. Whenever possible, only fresh herbs are to be used. In winter, herb vinegar and dried fruits are useful

According to Keining and Hopf, in acute cutaneous manifestations it

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199. BOMMER, S.: Deutsche med. Wchnschr. 58: 91, 1932.
200. LANGER, E.: Dermat. Wchnschr. 94: 483, 1932.
201. SCHUBERT, E.: Deutsche Ärtzte-Zeitung p. 341, 1932.

is advisable to increase the amounts of potassium, calcium, and magnesium in the diet, while the sodium is kept at a low level, by adding a salt mixture called Cationorm* consisting of compounds of the first three cations. This is supposed to expedite the regression of the skin manifestations.

While the Titro Dietetic Salt therapy received some clinical support, as already noted, it was rejected by other investigators because this salt contains about 85 per cent sodium chloride. Further studies will be necessary before this difference in opinion can be decided.

Table 22.—*Sample Menu for the Sauerbruch-Herrmannsdorfer Diet*

The meals should be served at the following hours:

7 a.m.	Porridge made from 250 cc. (8 oz.) of milk and oatmeal, rice, farina, tapioca, or millet; half an egg; 10 Gm. (⅓ oz.) of butter; sugar; lemon, cinnamon, or vanilla
9 a.m.	Weak coffee with plenty of milk or, if preferred, cocoa and milk or tea and milk; bread and butter, marmalade, or honey; uncooked vegetables such as carrots, kohlrabi, cauliflower, cucumber, sour dock, celery, radish, tomatoes, green peas, and corn on the cob
10 a.m.	Patients with irritable stomach may take a cup of expressed raw vegetable juice in place of the uncooked vegetables. Patients who are weak or seriously ill may take a little egg yolk mixed with lemon juice
Noon	A little soup; ripe fruit; in winter, stewed fruit
3 p.m.	Cream with a little or tea; fruit cake or cookies or zwieback or bread with butter, marmalade, or honey
5.30 p.m.	Dish of vegetable; fruit
8 p.m.	Porridge as in the morning; on hot summer days, sour milk; 1,000 to 1,500 cc. (2 to 3 pints) of milk during the day as well as the largest possible quantity of raw fruits and vegetables

D. LOW CARBOHYDRATE DIET

Low carbohydrate diets are used for two totally different purposes in dermatology: (1) to promote dehydration in inflammatory dermatoses, and (2) to treat diabetic skin diseases.

Adlersberg and Porges[171] have pointed out that a low carbohydrate, high fat diet furthers dehydration in a similar manner and to the same extent as a low salt diet. Volk[202] stated that in lupus vulgaris this form of dietary containing carbohydrates 50 to 60 Gm., protein 60 to 80 Gm., fat about 200 Gm., and salt ad libitum, and the Sauerbruch-Herrmannsdorfer diet can yield virtually identically good results. However, he adds that in some instances the specific foci respond too strongly. In these patients there are tremendous reactions, with marked necrotizing inflammation in the

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* Nordmark Chemical Works, Inc., New York, N. Y.

202. Volk, R.: Wien. klin. Wchnschr. 46: 763, 1933.

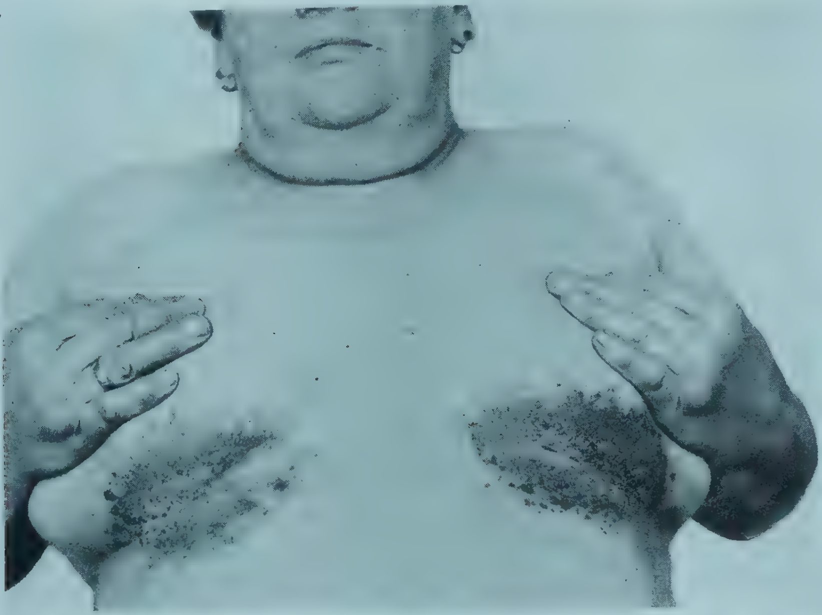

Fig. 5. Submammary Intertriginous Dermatitis on a Diabetic Basis

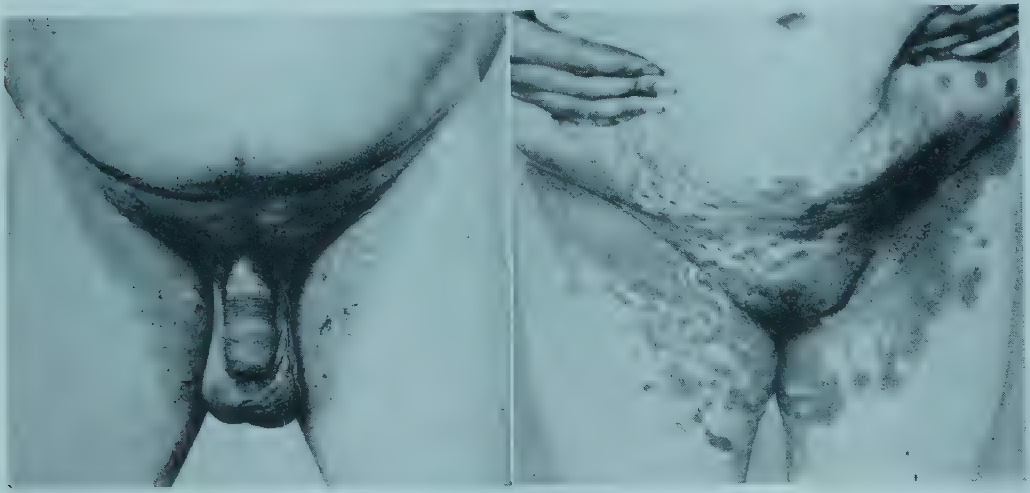

Fig. 6 Fig. 7

Chronic Inguinal Dermatitis Due to Diabetes

Fig. 6. Chronic dermatitis of ten years' duration in a 52 year old man, involving the inguinal, genital, perianal, and inner thigh areas. Fasting blood sugar 152 mg. per cent, glycosuria present. Marked improvement on diabetic regimen and insulin.

Fig. 7. Weeping dermatitis in a 69 year old woman who had shown a tendency to this condition for thirteen years. Glycosuria absent. Fasting blood sugar normal, but pathologic blood sugar tolerance curve.

Fasting	102 mg. per cent
After ½ hour	206 mg. per cent
After 1 hour	185 mg. per cent
After 2 hours	174 mg. per cent
After 3 hours	153 mg. per cent

affected areas, and pain and fever after three to four weeks of a low carbohydrate dietary. The inflammatory manifestations regress when the patient is restored to a normal diet. As a result of the necrosis, broad areas of the lupus heal with good cosmetic results.

The greatest usefulness of the low carbohydrate diet is, of course, in the management of dermatoses which are due wholly or in part to a reduction of carbohydrate tolerance. In this category are included certain types of dermatitis, notably those localized in the intertriginous zones (submammary [Fig. 5], inguinal [Figs. 6, 7], scrotal [Fig. 8], and intergluteal) and in the areas surrounding the excretory orifices such as balanitis (Fig. 9) (often leading to phimosis [Fig. 10]), circumoral and vulvar dermatitis; staphylococcal infections, including folliculitis, furunculosis (Fig. 11), carbuncles, ecthyma, pyoderma, sweat gland abscesses; mycotic infections (Fig. 12), especially monilia (Fig. 13) (here again chiefly those localized in the intertriginous zones); many cases of pruritus, particularly pruritus vulvae; some cases of urticaria and purpura; xanthosis; certain forms of xanthelasma (xanthoma); necrobiosis lipoidica diabeticorum (Fig. 14); ulcers (Figs. 15, 16); gangrene of the fingers (Fig. 18), toes (Fig. 17), or scrotum (Fig. 19).

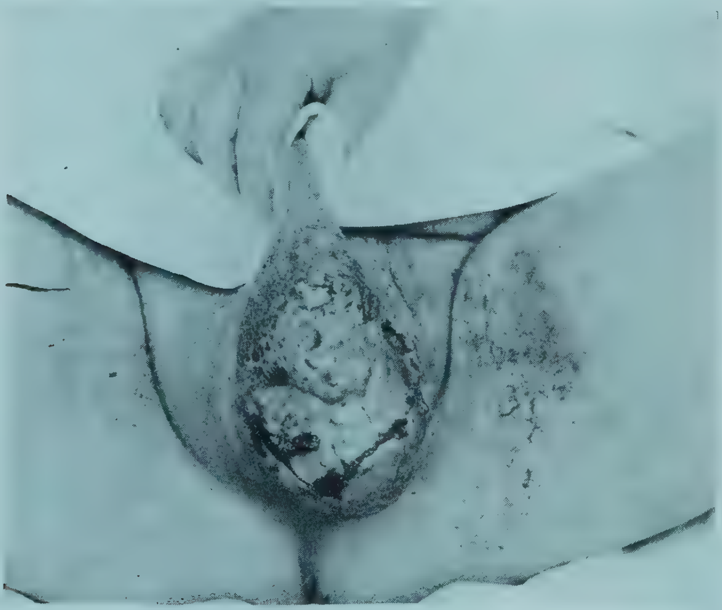

Fig. 8. Severe Scrotal Dermatitis Due to Diabetes

The face, hands, and feet of diabetics frequently show diffuse areas of redness, termed rubeosis, which is due to the color of the dilated superficial cutaneous venous plexus, seen through the skin. However, a mild degree of pallor characterizes the skin of many diabetic patients. According to Duncan,[203] this may be attributable in part to the elevation of the blood lipids, but in most instances it is due to advanced disease of the arteries. Even changes in the epidermal appendages, such as the nails and hairs, are often observed.

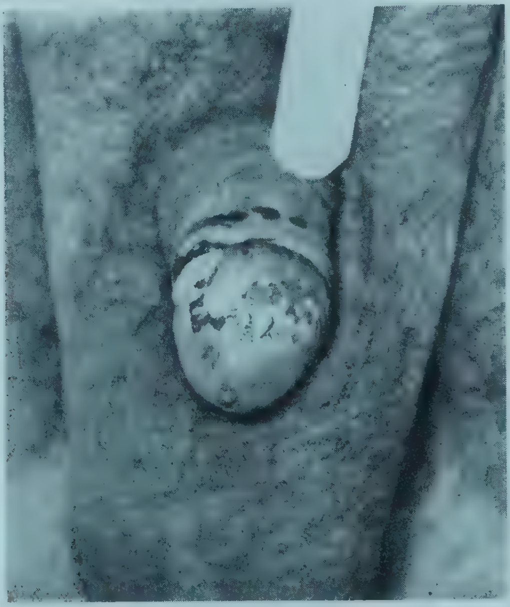

Fig. 9. Balanitis of Diabetic Origin

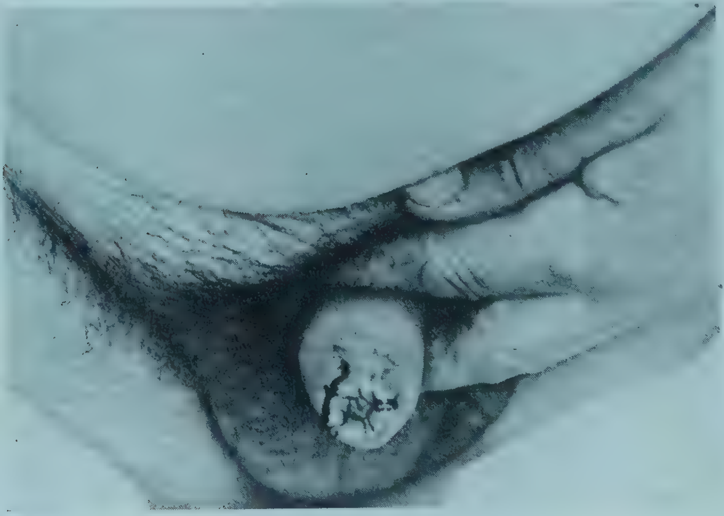

Fig. 10. Phimosis on a Diabetic Basis

That the possibility of diabetic etiology of a given dermatosis must always be borne in mind is shown by the statistics published by von Noorden and Isaac.[204] In their material, which consists of 25,000 diabetics,

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[203] Duncan, G. G.: Diseases of Metabolism. Philadelphia: Saunders, 1942.

[204] von Noorden, C. H. and Isaac, S.: Die Zuckerkrankheit und ihre Behandlung. Berlin: Springer, 1927.

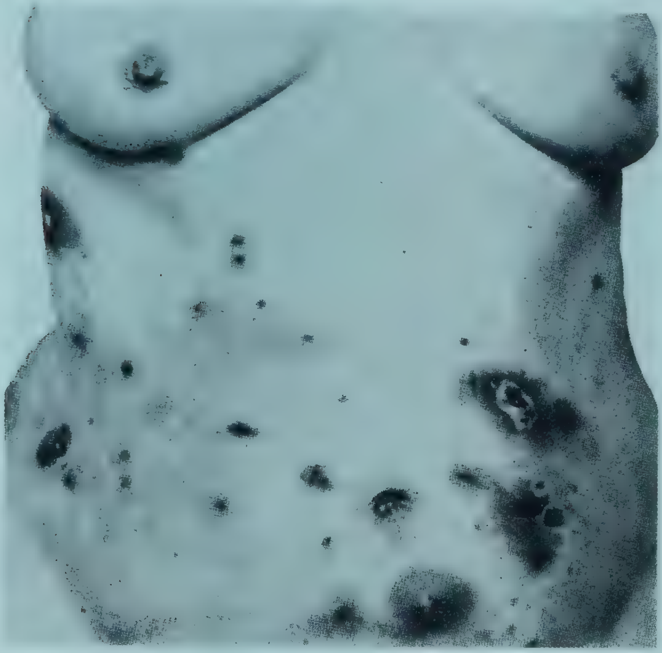

FIG. 11. FURUNCULOSIS ON THE BASIS OF LATENT DIABETES

	Blood sugar in mg. per cent	Glycosuria
Fasting	100	negative
After ½ hour	272	negative
After 1 hour	288	positive
After 2 hours	165	positive
After 3 hours	97	positive

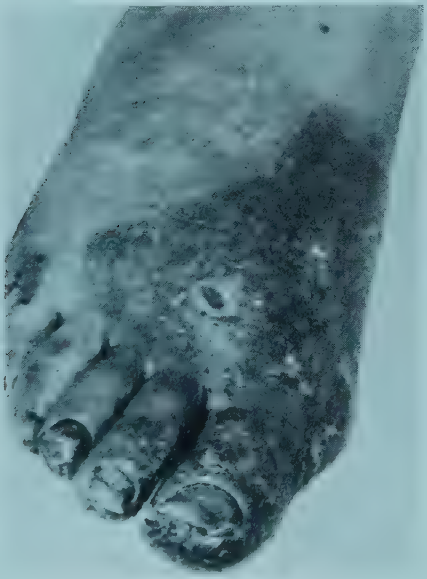

FIG. 12

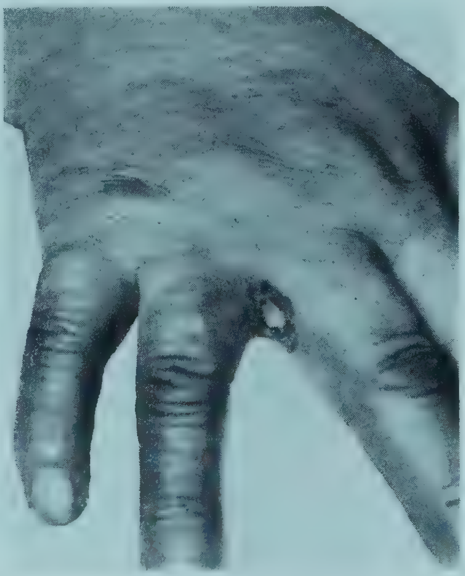

FIG. 13

FIG. 12. MYCOTIC DERMATITIS IN A DIABETIC PATIENT
FIG. 13. INTERDIGITAL MONILIASIS ON A DIABETIC BASIS

21.5 per cent of the cases suffered from pruritus at one time or another, while in a group of patients over 50 years of age, from 5 to 8 per cent presented refractory dermatitis and 10 per cent had furunculosis, carbuncles, or acneiform eruptions. According to Greenwood,[205] who studied

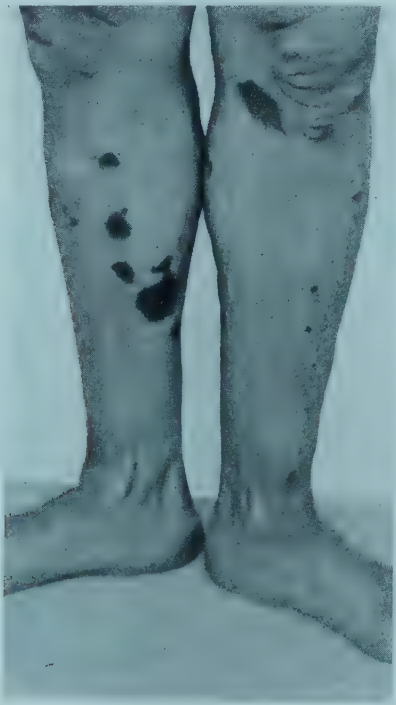

FIG. 14. NECROBIOSIS LIPOIDICA DIABETICORUM

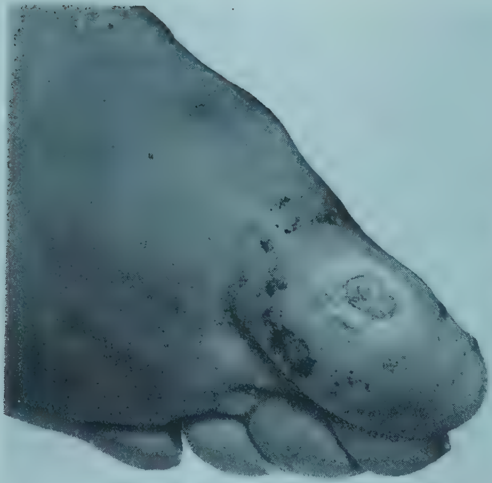

FIG. 15

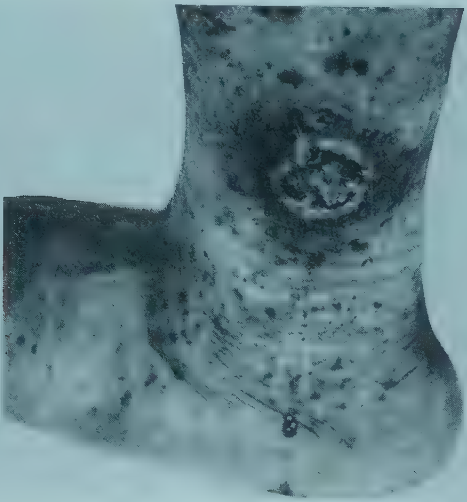

FIG. 16

ULCERS OF DIABETIC ORIGIN

FIG. 15. Simulating syphilitic malum perforans of the great toe.
FIG. 16. Simulating varicose ulcer of the leg.

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205. GREENWOOD, A. M.: J. A. M. A. 89: 774, 1927.

the skin in 500 cases of diabetes at Dr. Joslin's clinic, diabetic patients show a higher incidence of skin infections than nondiabetics. This is corroborated by the investigations of Pillsbury and Sternberg,[163] who demonstrated that the course of experimental skin infections is more severe in dogs on a high carbohydrate intake than in those on a low carbohydrate diet.

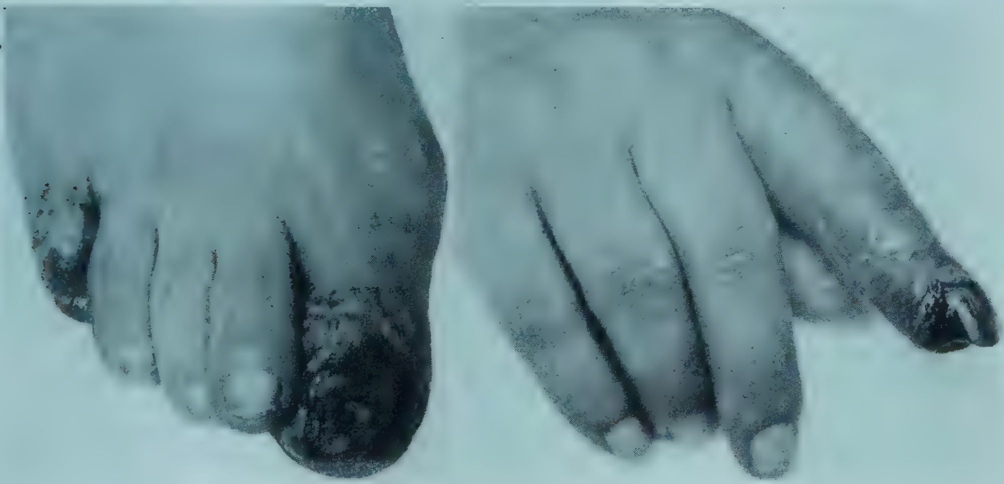
FIG. 17 FIG. 18

GANGRENE OF DIABETIC ORIGIN

FIG. 17. Gangrene of the toes.
FIG. 18. Gangrene of the finger.

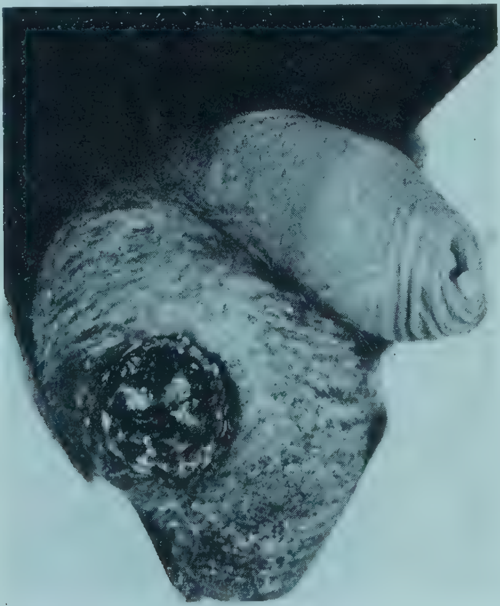
FIG. 19. GANGRENE OF THE SCROTUM

While it has been known for some time that there is a definite connection between frank diabetes and the skin diseases mentioned above, it is not yet generally recognized that frequently diabetes can also be the underlying cause of skin conditions which are not accompanied by glycosuria or which may even show normal fasting blood sugar levels. Therefore, in order to determine whether a given skin condition is due to diabetes it is necessary to do a blood sugar tolerance test. This procedure should be followed in every case in which there is reason to suspect diabetes, even when the fasting blood sugar is normal and there is no glycosuria. Ayres, Jr.,[206] Campbell and Burgess,[207] Haldin-Davis, and Wills,[208] and other authors are of the same opinion.

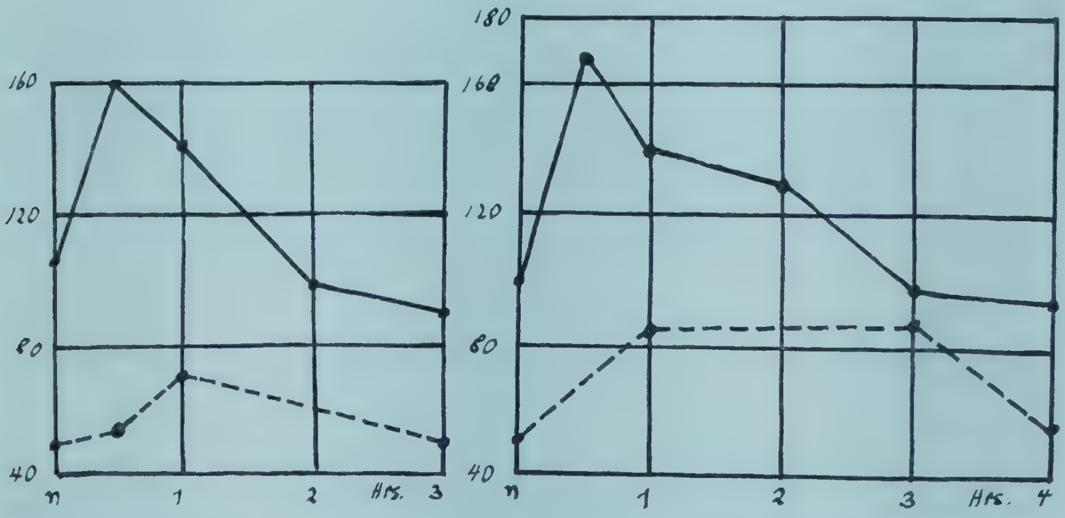

Fig. 20

Fig. 21

Figs. 20 and 21. Types of Normal Blood Sugar and Skin Sugar Tolerance Curves

The peak of the blood sugar curve is reached in one-half hour, with a return to the original level in two to three hours.

The peak of the skin sugar curve is reached in one hour with a return to the original level in three to four hours.

In doing the blood sugar tolerance test[209] we prefer the oral to the intravenous method because the former, which comes closer to reproducing the ordinary conditions of carbohydrate ingestion, constitutes the better functional test of the pancreas. In cases presenting secretory or motor disturbances of the gastrointestinal tract, Ottenstein[210] favors the intravenous over the oral method because in these conditions sugar resorption may be affected.

It should be particularly noted, however, that symptoms of hyper-

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[206] Ayres, S., Jr.: Arch. Dermat. & Syph. **11:** 623, 1925.

[207] Campbell, G. G. and Burgess, J. F.: Brit. J. Dermat. **39:** 187, 1927.

[208] Haldin-Davis, H. and Wills, L.: Brit. J. Dermat. **37:** 364, 1925.

[209] Urbach, E.: Klin. Wchnschr. **11:** 1789, 1932.

[210] Ottenstein, B.: Arch. f. Dermat. u. Syph. **158:** 691, 1929.

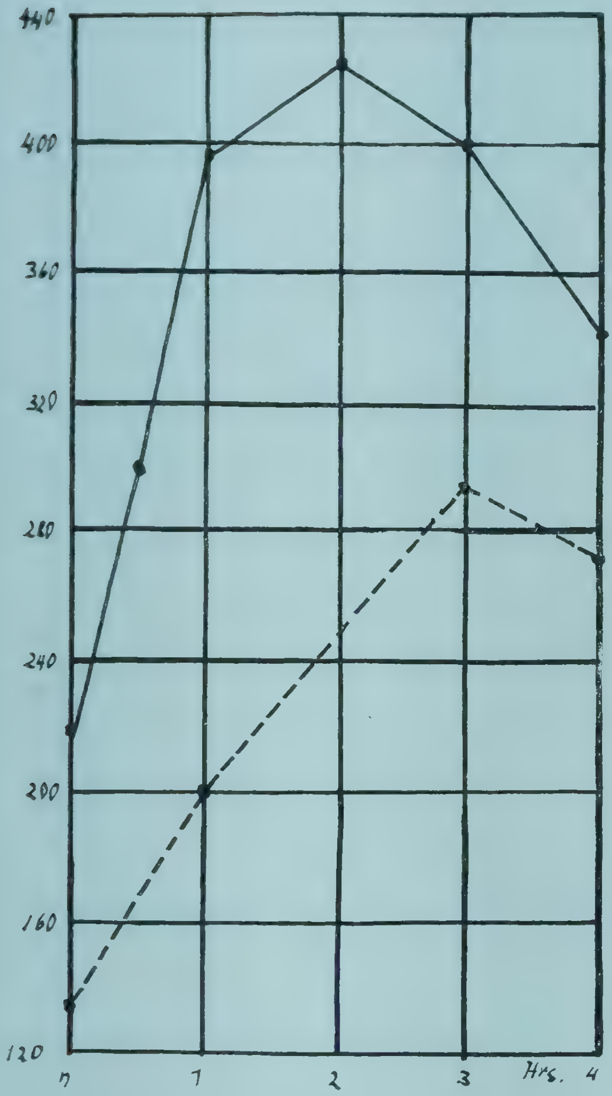

FIG. 22

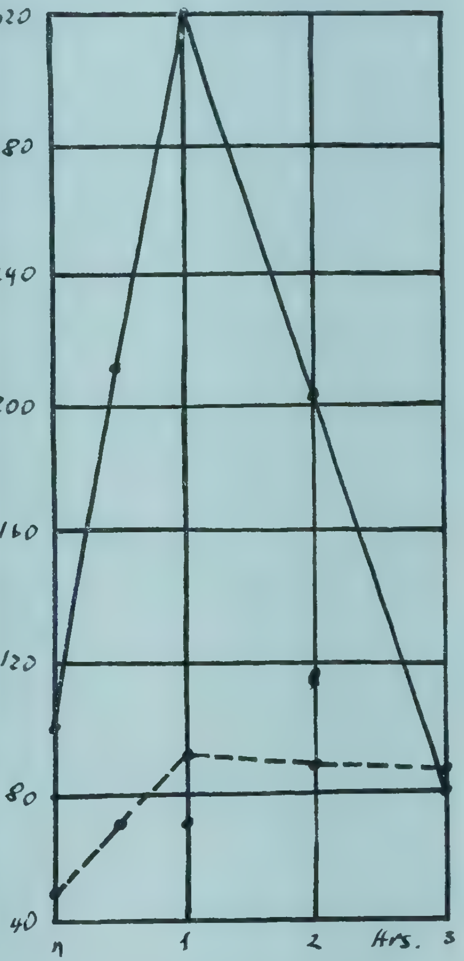

FIG. 23

FIG. 22. BLOOD SUGAR AND SKIN SUGAR TOLERANCE CURVES IN FRANK DIABETES

The peak of the blood sugar tolerance curve is delayed until two hours after the sugar meal; the decline of the curve is definite but slow. The peak of the skin sugar tolerance curve is delayed until three hours after the sugar meal; the decline of the curve is extremely slow.

FIG. 23. SYMPATHETIC-ENDOCRINE BLOOD SUGAR TOLERANCE CURVE

The blood sugar curve is very characteristic in that the fasting level is normal, the peak is reached in one hour, is markedly hyperglycemic but drops below the starting point in three hours. Note that the skin sugar tolerance curve does not follow the blood sugar pattern but is normal.

glycemia and a hyperglycemic response after a sugar meal do not in themselves by any means warrant the diagnosis of a disturbance in sugar tolerance due to hypofunction of the pancreas, since functional and organic disturbances of the endocrine-sympathetic system are also capable of affecting not only the fasting blood sugar but especially the blood sugar tolerance curve, creating a picture somewhat similar to that of diabetes. A blood sugar curve may be regarded as truly diabetic if it presents the three following departures from the normal: (1) Instead of reaching its peak within the first thirty to sixty minutes (Figs. 20, 21) the curve attains its highest point at some time during the second or third hour (Fig. 22). (2) After reaching its peak, the curve does not show a sharp and rapid decline as it does in normal subjects, but drops gradually and slowly. (3) It takes at least four hours instead of the normal two or three hours for the curve to reach its original level (Fig. 22). On the other hand a very quick rise of the blood sugar followed by a steep fall after three hours, not accompanied by a similar movement of the skin sugar, is considered by the present writer as a sympathetic-endocrine form of blood sugar reaction (Fig. 23).

TABLE 23.—*Difference Between Sympathetic-Endocrine and Diabetic Blood Sugar Curves*

	Sympathetic-Endocrine	Diabetes
Time of peak	30–60 minutes	2 to 3 hours
Shape of curve	sharp rise, steep fall	flat, with prolonged gradual decline
Return to starting level	in 2 to 3 hours	at least 4 hours
Hypoglycemia	may occur	does not occur

Differentiation between a diabetic (Fig. 22) and a sympathetic-endocrine blood sugar curve (Fig. 23) is a matter of considerable practical importance, since this may decide whether or not diabetic diet and possibly also insulin are to be prescribed (see also Table 23).

The same considerations apply to the skin sugar* as to the blood sugar. When glucose (100 Gm.) is given by mouth, the maximal level in the blood is reached within half an hour, while the maximal concentration in the skin is not observed before an hour after administration. In those cases in which the blood sugar returns to its original level within two hours, it takes the skin sugar curve three hours to drop to its starting point; and this takes even an hour longer in those not uncommon cases in which the blood itself requires three hours to show a decline in hyperglycemia (Figs. 20, 21).

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* In order to determine the quantity of sugar in minute tissue particles (weighing about 30 mg.) the writer[11] introduced the electric punch-biopsy method by which skin can be removed almost painlessly, without anesthetics of any kind, even when the procedure is performed repeatedly for a series of studies.

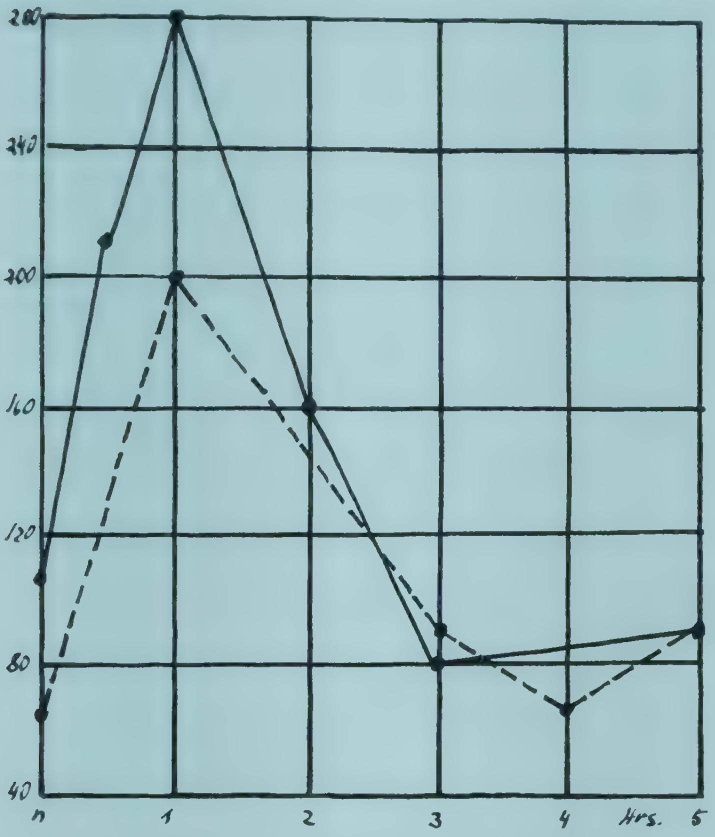

FIG. 24

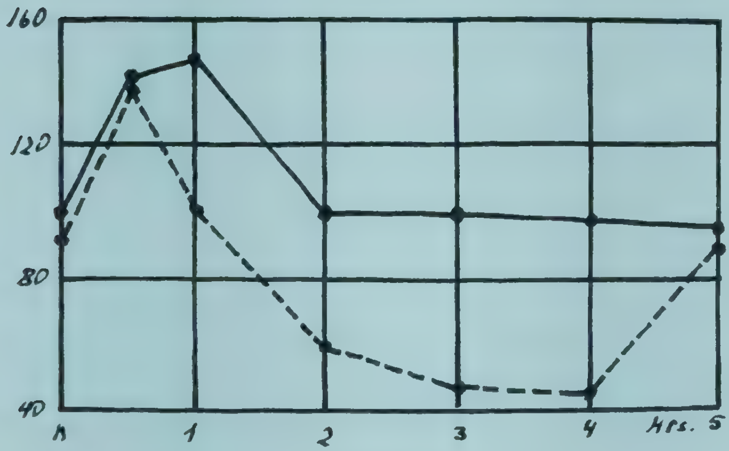

FIG. 25

EFFECT OF DIET ON THE BLOOD AND SKIN SUGAR TOLERANCE CURVES IN A DOG

FIG. 24. After one week of exclusive meat diet.

FIG. 25. After one week of a pure carbohydrate diet.

The diabetic skin sugar curve in man (Fig. 22) shows certain typical peculiarities. The peak of the rise in diabetics is generally not reached until well toward the end of the third hour. It is still very high after four hours, even in those cases in which the blood sugar has definitely begun to drop by this time.

Although the blood sugar tolerance test is generally of the utmost importance in the diagnosis of skin diseases due to diabetes, it is unreliable in some isolated instances, as revealed by the high fasting skin sugar level or by a diabetic type of skin sugar tolerance curve but with normal blood sugar curve.

As has been shown by Uchida,[211] Adlersberg and Porges,[171] Himsworth,[212] and other authors with regard to the blood, and by Urbach[11] with regard to the skin, the course of the blood and skin sugar curves after a sugar meal is also affected by the nature of the preceding diet. Thus, dogs that have been on a high protein, virtually carbohydrate-free diet will show a marked rise in blood and skin sugar levels following administration of a sugar meal (Fig. 24). When the same animals have been previously fed a purely carbohydrate diet they respond to the same sugar meal with normal increases in the blood and skin sugar levels (Fig. 25). This experiment is of practical significance since it demonstrates that sugar tolerance tests should never be performed in subjects previously on a low carbohydrate diet, if such a procedure is to have any diagnostic value. As a result of a preceding diet low in carbohydrates a distortion of the sugar tolerance curves of the blood and the skin may erroneously suggest a pathologic sugar metabolism.

In animals with experimentally induced diabetes the sugar level of the skin rises considerably above that of the blood and has a tendency to rise even after four hours (Fig. 26).

Depending on the behavior of the fasting blood and fasting skin sugar levels and particularly the blood and skin sugar tolerance test, we can divide skin diseases due to disturbed carbohydrate tolerance into five distinct groups:

1. Skin diseases in frankly diabetic individuals as evidenced by fasting hyperglycemia.
2. Dermatoses in individuals with latent diabetes, in whom the nature of the disease can be demonstrated only by means of the sugar tolerance test.
3. Dermatoses in individuals with normal fasting blood sugar but with high fasting skin sugar levels (cutaneous glycohistechia,* or skin diabetes).
4. Skin diseases in individuals who may present an atypical blood sugar curve, but who are nevertheless not diabetic, as demonstrated by the normal skin sugar curve.

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* Greek: *γλυκυς* = sweet, *ἱστίον* = time, *ἔχειν* = to hold.

211. Uchida, K.: Biochem. Ztschr. **194:** 111, 1928.
212. Himsworth, H. P.: Clin. Sc. **1:** 251, 1934.

5. Skin diseases which are not the result but the cause of increased blood and skin sugar levels, as demonstrated by the fact that both curves return to normal after the dermatosis has been cured by external therapy.

In the first group the blood and skin sugar curves show the typical diabetic contours mentioned above and as exemplified in Figs. 20 and 21.

Group 2 comprises the cases in which the fasting blood and skin sugars appear normal, but in which sugar tolerance tests reveal a diabetic curve. The possibility of latent diabetes should always be borne in mind when the dermatosis presents unusual symptoms such as inordinate severity or extent (e.g., of a dermatitis or furunculosis), unusual localization (e.g., a dermatitis in the genital regions or in intertriginous areas, fissures in the corners of the mouth, or pruritus vulvae), failure of the usual therapeutic measures, or when the clinical characters of the patient (habitus, age, race) arouse our suspicion. Obese individuals over 50 years of age, with a somewhat purplish red complexion, are likely to have latent diabetes, especially if they are of Jewish parentage.

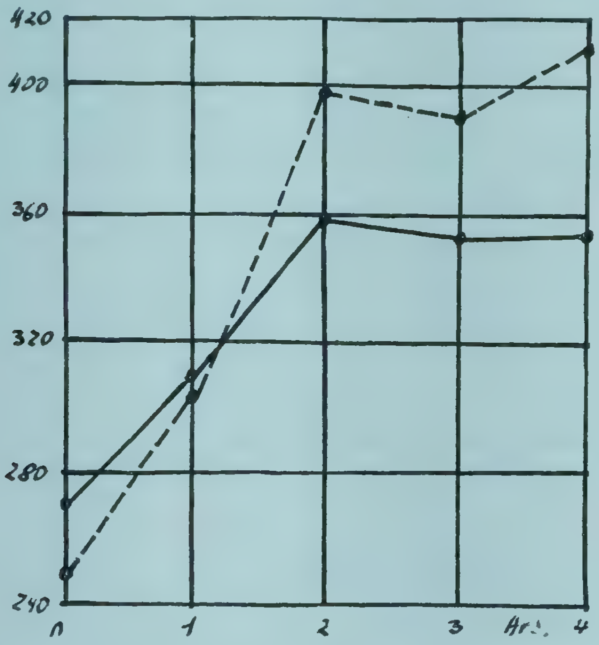

FIG. 26. BLOOD SUGAR AND SKIN SUGAR TOLERANCE CURVES IN A DOG ONE WEEK AFTER PANCREATECTOMY

As an example, we present the case of an obese woman of 32, who had been suffering from severe urticaria for many months. The sugar tolerance test, while starting with normal blood and skin sugar values (Fig. 27), showed a typical diabetic response. Elimination of carbohydrates from the diet for twenty-four hours caused the urticaria to disappear, while it reappeared three hours after three pieces of sugar had been taken in tea. The patient presented no manifestations so long as she adhered to a carbohydrate-free diet.

Similar circumstances have been encountered in a few cases of pruritus and anal dermatitis, furunculosis, and sweat gland abscesses.

Group 3 comprises the relatively rare cases in which the blood sugar values are normal, while the skin sugar level is well above normal. This discrepancy becomes even more marked following a sugar tolerance test, when the skin sugar curve alone becomes pathologic. This phenomenon is called "cutaneous glycohistechia," or skin diabetes. In view of the fact that in these patients diabetic management serves to bring the skin sugar levels down to normal and to clear up the cutaneous condition, and that a diet rich in carbohydrates brings on a recurrence of the disease manifestations, we feel justified in assuming that cutaneous glycohistechia must be attributable to underlying diabetes.

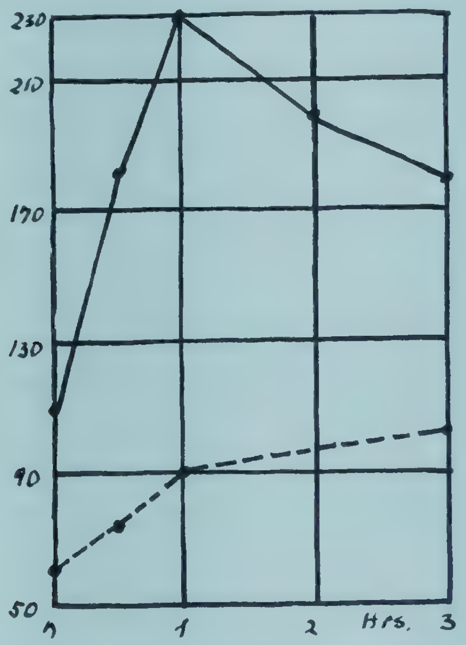

Fig. 27. Diabetic Type of Blood Sugar and Skin Sugar Tolerance Curves in a Case of Urticaria Due to Latent Diabetes

The following case report may serve to illustrate these statements.

A woman, 52 years of age, suffered from an extensive subacute dermatitis of the body, which failed to yield to many weeks of painstaking treatment in a hospital. The blood sugar tolerance test was completely normal, as is shown in Fig. 28. The skin sugar tolerance curve began with a slightly increased fasting level (68 mg. per cent); reached its peak (128 mg. per cent) after an hour; was still quite high (108 mg. per cent) after three hours, when the blood had begun to show hypoglycemic levels; and had not returned to its initial level by the end of the fourth hour. Institution of a low carbohydrate diet together with small doses of insulin brought about speedy

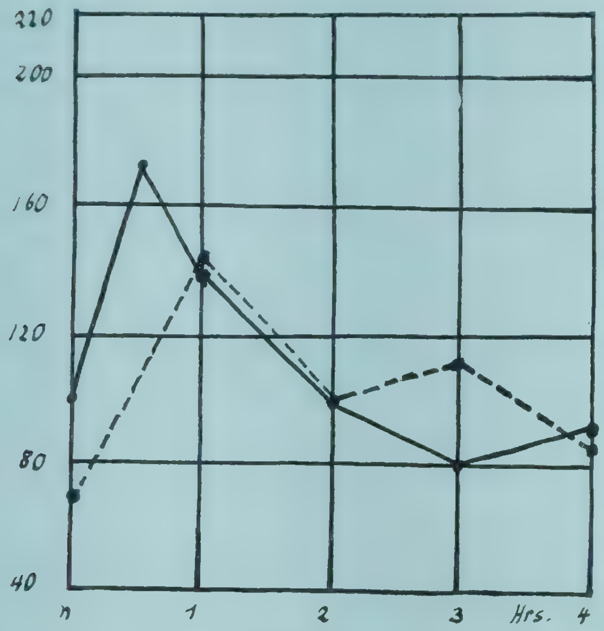

FIG. 28

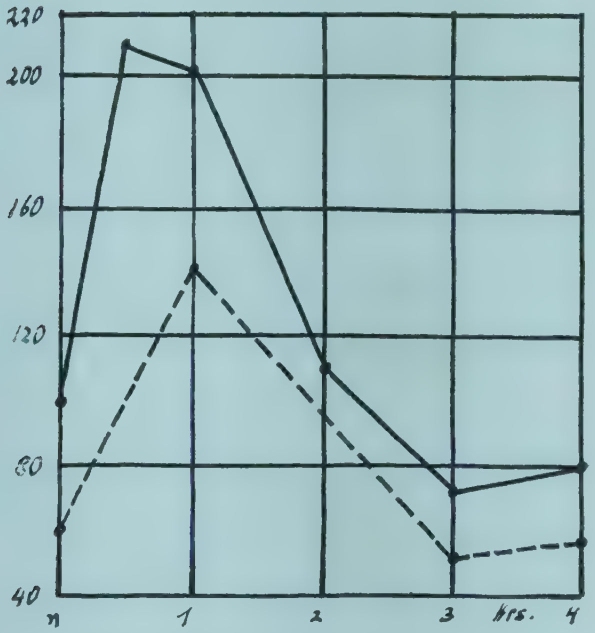

FIG. 29

BLOOD SUGAR AND SKIN SUGAR TOLERANCE CURVES IN A CASE OF DERMATITIS CAUSED BY SKIN DIABETES (HYPERGLYCODERMIA WITHOUT HYPERGLYCEMIA)

FIG. 28. On a normal diet the patient showed a pathologic skin sugar tolerance curve, marked by a very slow decline, but normal blood sugar curve.

FIG. 29. On a very low carbohydrate, high protein, moderate fat regimen the skin sugar tolerance curve became normal and the patient showed marked clinical improvement.

improvement of the dermatitis. In conformity with the clinical improvement, the fasting skin sugar level was normal (59 mg. per cent) after a week, while the blood sugar level was virtually unchanged (100 mg. per cent). Furthermore, the clinical improvement was paralleled by the change in the skin sugar tolerance test, inasmuch as the skin sugar now dropped to a point below its initial level by the end of the third hour (Fig. 29). Strict observance of the low carbohydrate diet alone caused the skin manifestations to disappear completely; however, they recurred when the diet was not strictly adhered to. This case is noteworthy because of the fact that exacerbations of the dermatitic manifestations could invariably be cleared up by means of dietary adjustments and insulin, without any kind of local treatment.

Group 4 comprises the dermatoses in which the sugar tolerance test shows an enormous rise in the blood sugar level, which returns to normal, however, after three hours. The skin sugar curve (Fig. 23), in contrast to the blood sugar curve, is normal in these cases. Table 23 clearly illustrates the difference between sympathetic-endocrine and diabetic skin sugar curves. In the former there is nothing like the excessive rise shown by the blood sugar curve; the peak is reached during the first hour, and the level returns to normal between the third and fourth hours. The diabetic skin sugar curve shows considerably higher fasting levels to begin with; it does not reach its much higher peak, however, until the third hour; and it takes five hours or more to return to its normal level.

We encountered such atypical blood sugar curves notably in severe ulcera cruris, in a case of pyodermia chronica ulcerosa, in several cases of urticaria, and in other dermatoses. A common characteristic of these various conditions was their therapeutic refractoriness to a low carbohydrate diet, prolonged insulin administration, and local application of insulin to the ulcers. Therefore, in conformity with the normal skin sugar curve after a sugar tolerance test, we feel justified in attributing these pathologic blood sugar curves, not to a decrease in sugar tolerance, but to an excessive mobilization of glucose, probably due to endocrine and/or sympathetic influences.

We consider it of great clinical significance that the cases in this group show no improvement whatsoever when put on a low carbohydrate diet and given a long course of treatment with insulin.

Group 5 comprises disturbances of the carbohydrate metabolism, as evidenced by elevated fasting blood sugar and skin sugar levels and by pathologic blood sugar and skin sugar curves, and attributable to an extensive experimental dermatitis of chemical or mechanical origin. They were first demonstrated by Miyake and associates.[213]

According to these authors, the blood and skin sugars are increased because the severe inflammation of the skin leads to the formation of by-products which affect the cells of the liver either directly or by way of the nervous system and thus bring about an insufficiency of the carbohydrate metabolism.

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[213] MIYAKE, I. and NARAHARA, K.: Jap. J. Dermat. & Urol. **30:** 85, 1930.

The results of these animal experiments seem to conform perfectly with those obtained by Moncorps,[214] Milbradt,[117] and Marchionini[215] in their studies in man. Their investigations reveal that intensive ultraviolet irradiation is followed by a rise in the skin sugar and blood sugar levels and by pathoglycemic sugar tolerance curves.

Noteworthy in this connection are the observations reported by Ayres,[206] Schmidt,[216] Whitfield,[217] and others that pyogenic infections decrease the patient's dextrose tolerance, or at least decrease the rate at which sugar is removed from the blood stream and the tissues. After the dermatosis has cleared up under suitable external treatment, it is often found that the blood sugar level has returned to normal. In animal experiments Nicholson and Holman[218] demonstrated that staphylococcal skin infections produced a definite although temporary decrease in carbohydrate tolerance in rabbits, with glucose tolerance curves similar to those seen in mild diabetes.

In summary of this group it may be said, therefore, that, in human beings and animals alike, extensive inflammations of the skin can exert an influence on the carbohydrate metabolism; this means that this metabolic disturbance may fundamentally be of peripheral origin. As yet, very little is known as to the precise manner in which the periphery (e.g., the skin) exerts its influence on metabolism, whether this takes place as a result of an influx of nitrogen or uric acid released in the skin due to increased nuclear disintegration, or indirectly via endocrine glands or via the vegetative nervous system. However, some authors have derived substances from artificially inflamed skin which raise the blood sugar level and prolong the sugar tolerance curve. This would seem to demonstrate conclusively that the disturbances in the carbohydrate metabolism, which appear in the course of transient dermatoses and disappear when the skin manifestations clear up, are in no way connected with pancreatic diabetes.

The practical conclusion to be drawn from these observations is that great care must be taken in evaluating the pathoglycemic results with regard to the pathogenesis and therapy of extensive or infectious skin diseases. For it is only when diabetic treatment (diet and/or insulin) is followed by clinical improvement that the etiologic significance of the disturbance of the carbohydrate metabolism may be regarded as firmly

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214. Moncorps, C., Bohnstedt, R. M., and Schmid, R.: Arch. f. Dermat. u. Syph. **169:** 67, 1933.
215. Marchionini, A.: Med. Welt. **11:** 1197, 1937.
216. Schmidt, E. G., Eastland, J. S., and Burns, J. H.: Arch. Int. Med. **54:** 466, 1934.
217. Whitfield, A.: Delib. 9th Internat. Dermat. Congress **1:** 252, 1935.
218. Nicholson, T. F. and Holman, W. L.: Proc. Soc. Exper. Biol. & Med. **49:** 75, 1942.

established. Otherwise, the metabolic disturbance should be interpreted as a result of the skin disease.

While it has been demonstrated again and again that certain dermatoses are the consequence of a disturbance of carbohydrate metabolism, the nature of the pathogenesis involved is still a highly controversial question.

TABLE 24.—*Low Carbohydrate (Diabetic) Diet*

Purpose of the diet: Restriction of intake of carbohydrates to amounts compatible with the patient's ability to metabolize them, thus reducing the effects due to an overload of carbohydrates in the tissues.

Basic principles: The total daily caloric intake is determined on the basis of the patient's standard weight, his physical activity, and the severity of his diabetes. Where control of the diabetic status is impossible without reduction of caloric intake to levels approaching starvation, insulin is used to enhance the patient's ability to metabolize sugar. The carbohydrate tolerance is generally improved when the diet is relatively high in carbohydrates and low in fats.

The foods listed in this table as permitted are allowed only in amount and variety according to the patient's diabetic status.

PERMITTED AND PROHIBITED FOODS IN THE LOW CARBOHYDRATE (DIABETIC) DIET

Permitted

Carbohydrates	Proteins	Fats
Breadstuffs	Meats, lean	Butter
Cereals	Fish	Cream
Fruits	Poultry	Vegetable oils
Vegetables	Milk	Lard
	Cheese	Meat, fat
	Legumes	Egg yolk
	Egg white	Cheese
	Nuts	Nuts

Prohibited

Sugar, marmalade, honey, ice cream, candy and other confections, molasses, jams and preserves

A detailed list of food values will be found in the Appendix.

The following more or less well founded theories have been advanced to explain the connection:

1. The increased concentrations of sugar or of intermediary and incomplete products of carbohydrate metabolism in the skin act in one of three ways: by direct stimulation of the sensory nerves of the skin, causing pruritus; by creating a disturbance of the secretory and vasomotor nerves, resulting in anhydrosis, asteatosis, and xerosis of the skin; or by exerting a direct influence on the capillary walls and glands (Kaposi[219]).

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[219] KAPOSI, M.: Wien. med. Wchnschr. 34: 1, 1884.

TABLE 25.—*Sample Menu for the Low Carbohydrate (Diabetic) Diet*

Calculated on the basis of 30 calories per kilogram for a patient whose standard weight is 60 kilograms and who is a housewife.

Diet Prescription:

Carbohydrates	200 grams or 800 calories
Protein	60 grams or 240 calories
Fats	100 grams or 900 calories
Total	1,940 calories

Type of Food		Example	Content in Grams		
			C	P	F
Breakfast					
Bread	60 Gm.	2 slices	32	6	
Cereal prepared	20 Gm.	⅘ cup corn flakes	16	2	
Fruit, 10% group	150 Gm.	1 medium orange	15		
Eggs, boiled, poached, or coddled		2 small eggs		9	9
Bacon, crisp	5 Gm.	½ average slice		2	2.5
Cream, 20%	50 cc.	1⅔ oz.	2.5	1.5	9.5
Butter	14 Gm.	1 average pat			12
Coffee (no sugar)	no limit				
Lunch					
Bread	30 Gm.	1 slice	16	3	
Vegetable, 3%	100 Gm.	½ cup string beans	3	1	
Vegetable, 6%	100 Gm.	½ cup carrots	8	2	
Fruit, 10%	140 Gm.	1 large orange	14		
Potato, baked or boiled	100 Gm.	1 medium large potato	18	2	
Milk	200 cc.	⅚ cup	10	6	8
Meat, medium fat	25 Gm.			5	
Butter	25 Gm.	2 average pats		0.5	21
Coffee or tea (no sugar)	no limit				
Dinner					
Bread	30 Gm.	1 slice	16	3	
Vegetable soup (500 cc. clear broth 3% vegetable 50 Gm. 6% vegetable 25 Gm.)		1 recipe	3	1	
Vegetable, 6%	100 Gm.	½ cup squash	6	2	
Potato, baked or boiled	50 Gm.	size of 1 egg	9	1	
Fruit, 20%	150 Gm.	1½ bananas	30	1.5	1.5
Meat, medium fat	50 Gm.			10	
Cream, 20%	50 cc.	1⅔ oz.	2.5	1.5	9.5
Butter	14 Gm.	1 average pat			12
Coffee or tea (no sugar)	no limit				

2. J. Jadassohn[220] regards some of the skin diseases in diabetics as belonging to the group of the excretory dermatoses on the theory that the sugar passing through the secreting glands exerts a pathogenic influence on the cutaneous bacterial flora. Carrie and Koenig[221] have demonstrated that patients with high blood sugar levels excrete abnormally large amounts of sugar onto the skin surface.

3. Abnormal decomposition products of sugar bring about an *Umstimmung* (alteration of the terrain) as a result of which the skin reacts to endogenous and exogenous stimuli other than those derived from the abnormal sugar metabolism, with cutaneous manifestations (Bloch,[222] Achard[223]).

4. According to Stokes, Beerman, and Ingraham,[174] ingested carbohydrate may influence skin infections through its action on the bacterial content of the intestinal tract, causing vasomotor instability which constitutes a clinically important fact or predisposing to a wide variety of inflammatory reactions.

5. The influence of carbohydrate on skin infections may be exerted through its effect on the water balance of the tissues. It has been shown that a high carbohydrate intake leads to water retention in the tissues (Pillsbury and Sternberg[163]), while carbohydrate restriction results in dehydration followed by decreased susceptibility to experimentally induced skin infections (Kulchar and Alderson[178]).

6. Rudy and Hoffman[224] champion the theory that skin manifestations in diabetes mellitus are not related to the hyperglycemia but are attributable to the skin's increased vulnerability resulting from a deficiency in the components of the vitamin B complex, notably nicotinic acid. These authors, as well as Gross,[225] report that skin lesions, including those of monilia infections in diabetics, respond to treatment with vitamin B complex and with nicotinamide. However, since Neuwahl[226] has demonstrated that nicotinic acid improves the carbohydrate tolerance of diabetic patients and may enhance the action of insulin, the therapeutic effect of nicotinic acid and the explanation based on this effect may not quite conform with Rudy and Hoffman's views on the subject.

7. Skin disorders involving extensive dermatitis of chemical or mechanical origin may bring on a disturbance in the carbohydrate metabolism. This is generally interpreted as evidence of injury to the liver, rather than as a sign of disturbed pancreatic function (Milbradt[117]).

220. Jadassohn, J.: Delib. 5th Internat. Dermat. Congress **2:** 155, 1905.
221. Carrié, C. and Koenig, R.: Arch. f. Dermat. u. Syph. **173:** 611, 1936.
222. Bloch, B.: Ergeb. d. inn. Med. u. Kinderh. **2:** 521, 1908.
223. Achard, C.: Cinque lecons sur le diabete. Paris: Bailliere, 1925.
224. Rudy, A. and Hoffmann, R.: New England J. Med. **227:** 893, 1942.
225. Gross, P.: Arch. Dermat. & Syph. **43:** 504, 1941.
226. Neuwahl, F. J.: Lancet **2:** 348, 1943.

8. Lastly, Whitfield[217] alludes to the assumption that, in many bacterial infections, the thyroid-adrenal apparatus is brought into action as a part of the organism's defense mechanism. The resulting rise in the blood sugar is therefore an effect and not the cause of the skin disease in these cases.

Turning now to the management of skin diseases of diabetic origin, it is clear that the treatment of such cases is chiefly dietary. Table 24 gives a short résumé of the basic principles involved and Table 25 a sample menu for a low carbohydrate diet. In instances where the diet alone is inadequate to control the diabetes, insulin therapy is indicated.

E. LOW FAT DIET

In recent years diets low in animal and vegetable fat have been commonly prescribed for the treatment of certain dermatoses, notably the lipoidoses of the skin. The low fat diet has also been advocated in the treatment of psoriasis by Gruetz, in acne by Sutton, Jr., in seborrheic conditions of adults by Barber and the Suttons, and particularly those of childhood by Finkelstein. In addition, this type of dietary has proved effective as an adjuvant measure in the management of certain diabetic dermatoses. Lastly, it is prescribed in skin diseases which are connected, directly or indirectly, with hepatic disturbances, notably cirrhosis of the liver, or with cholecystitis (see p. 332).

The older literature contains numerous reports that, in man and in animals alike, ingested fat is in part taken up and eliminated by the sebaceous glands. Kuznitzky has noted in man the appearance in the sebaceous glands of ingested oil of sesame. Buschke and Fraenkel made a similar observation in rabbits and guinea pigs, in which the same oil was identified in the secretion of the meibomian glands. M. B. Schmidt was able to demonstrate the presence of ingested oil in the sebaceous secretion of white mice. Loehlein[227] described an orange red to gold yellow color of the fatty tissue of Cameroon Negroes due to consumption of palm oil. These clinical observations were verified only recently by Schoenheimer and his collaborators.[228, 229] They fed animals either fats or fatty acids labeled with isotopic hydrogen and then determined the concentration of the isotopic hydrogen in the lipids of the body. By this method they demonstrated that dietary lipids are rapidly and extensively deposited in the fat depots and in the fat of the internal organs. In a typical experiment[24] rats were fed a diet containing 6 per cent of butter to which was added about one tenth as much of an experimental fat in the form of isotopic palmitic acid, which naturally merged during absorption with the ordinary palmitic acid of the butter. After eight days of such feeding, the body fat was found to contain almost half of the tagged fatty acid that had been fed.

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[227] LOEHLEIN, M.: Deutsche med. Wchnschr. **37:** 305, 1911.
[228] RITTENBERG, D. and SCHOENHEIMER, R.: J. Biol. Chem. **121:** 235, 1937.
[229] RITTENBERG, D., SCHOEHHEINER, R., and EVANS, E. A., JR.. J. Biol. Chem. **120:** 503, 1937.

The influence of the ingested food fat on the composition of the stored fat is best illustrated by the "soft pork" problem. When hogs are fattened on food containing a high percentage of low melting fat or oil, such as the "cake" from the separation of peanut, soybean, or cottonseed oil, the dressed meat is soft and oily and therefore undesirable. On the other hand, hogs fed on grain fodder form a firm, high melting point fat from the carbohydrates (Ellis and co-workers,[230] Longenecker[231]).

The experimental work of Pollicard and Tritchovitch[232] is also highly enlightening. These authors showed that scarlet red, when given by mouth together with food, produces vital staining of the depot fat in the subcutaneous tissues and omentum, the composition of this stored fat depending very largely on that of the lipids ingested. It was observed, however, that the tissue fat of the various organs was not stained. If the animal is starved the colored depot fat disappears, and with it the coloring dye. These authors demonstrated, moreover, that the cells of the sebaceous glands normally elaborate their fatty secretion from the fatty acids circulating in the blood. This is a process of true cellular activity. However, these cells are also capable of taking up the lipid particles that circulate in the blood, especially after digestion. These particles, unlike the normal sebaceous secretion, are colored after ingestion of scarlet red. They are found extending to the periphery of the gland, in close contact with the capillaries; the normal sebaceous fat, in contrast, is localized in the center of the gland, near the duct. Thus, the normal function of the sebaceous glands is adipogenesis, the manufactured fat having a special composition of its own. Under certain conditions—for example, in animals after hyperalimentation—the sebaceous glands assume the function of adipopexy (fat fixation), in which case the fat taken up directly from the blood may be of the same character as the ingested fat. These observations make it easy to understand how the normal sebaceous secretion may be altered either by an excessive intake of fat or fat-forming foods, or by ingestion of special forms of fat.

Although a low fat diet is strikingly effective in various dermatoses, as will be discussed in detail below, prolonged use of an extremely low fat diet is inadvisable. Burr and Burr[17] found that unsaturated fatty acids are essential for the proper nutrition of rats. Young rats placed on a diet extremely low in fat, and thereby lacking certain essential fatty acids, soon manifest several characteristic abnormalities, namely, severe dandruff, scaliness of the feet and tail, retardation of growth, purpura, hematuria,

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230. Spadola, J. M. and Ellis, N. R.: J. Biol. Chem. **113:** 205, 1936.
231. Longenecker, H. E.: Biol. Symposia **5:** 99. 1941.
232. Policard, A. and Tritchovitch, Y.: Lyon Med. **131:** 981, 1922.

and premature death. Administration of very small quantities of the essential unsaturated fatty acids or their esters results in the rapid disappearance of all signs of the fat-deficiency disease. No such beneficial effects follow the ingestion of saturated fatty acids even in large amounts. Similar observations were reported by Hansen and Wiese.[233] When very young dogs were given a diet low in fat (0.13 per cent) which furnished only 1 per cent of the total calories but which otherwise normally included all the necessary vitamins, it was noted after about three months that the skin of the animals became dry and the hair dry and coarse. This was followed by a definite flaky desquamation with large scales and fine scurfy specks appearing over the entire body, but most marked on the ventral surface (Fig. 30). The skin and hair of the litter mates receiving 28 per cent of their calories as lard in the diet remained clear and soft (Fig. 31). Coincidental with the skin changes marked differences in the degree of unsaturation of the fatty acids of the blood serum were demonstrated. The most marked change in the iodine number of the fatty acids was found in the acetone-soluble fraction, the average value being 83.9 for the animals receiving practically no fat in contrast to 118.7 for the dogs getting lard in the diet (Hansen and Wiese[233]). Schneider[234] demonstrated

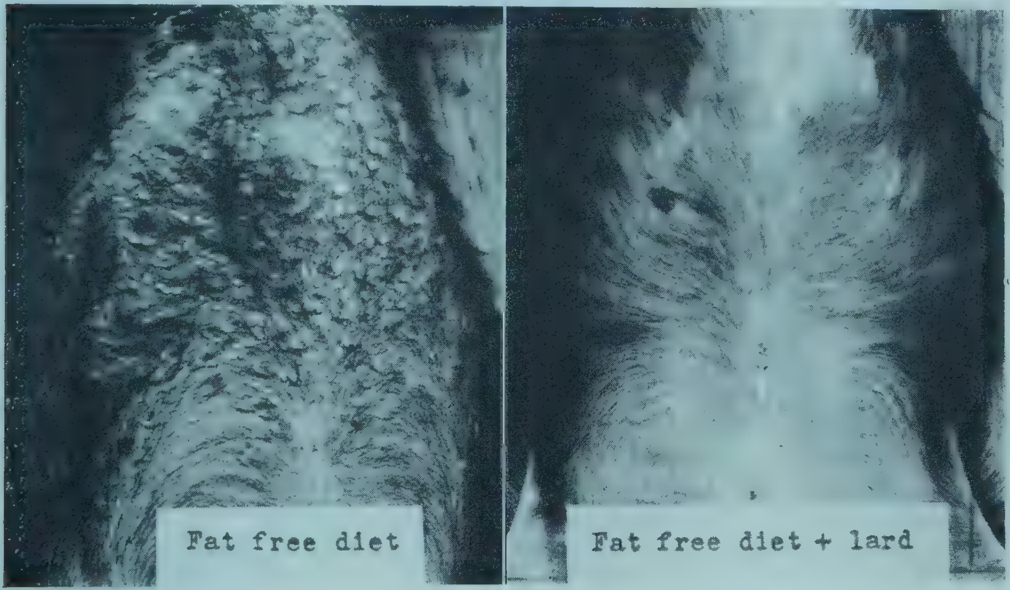

FIG. 30 FIG. 31

INFLUENCE OF DIETARY FAT ON THE SKIN OF DOGS

FIG. 30. Ventral surface of a puppy on a low fat diet.

FIG. 31. Litter mate control puppy receiving 28 per cent of the calories as lard.

(Courtesy of Drs. A. E. Hansen and H. F. Wiese and the Proc. Soc. Exper. Biol. & Med.)

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[233] HANSEN, A. E. and WIESE, H. F.: Proc. Soc. Exper. Biol. & Med. **52**: 205, 1943.

[234] SCHNEIDER, H. A.: Proc. Soc. Exper. Biol. & Med. **44**: 266, 1940.

the antidermatitis potency of fresh butter fat in rats; however, this activity is destroyed when the butter fat is allowed to become rancid. The skin of fat-deficient rats has been described with camera lucida drawings by Williamson.[235] Such animals have thicker and more differentiated epidermis, with the stratum granulosum becoming especially distinct and the horny layer broader. It should be added here (and it will be discussed in some detail on p. 181) that there must be vitamin B_6 (pyridoxine) in the food in addition to the essential fatty acids if the fat deficiency disease in rats, called rat acrodynia, is to be prevented.

According to the Burrs,[17] the most important essential fatty acid is arachidonic acid, although linoleic and linolenic acids are effective in curing the fat-deficiency diseases. While it is generally accepted that unsaturated fatty acids are necessary for the welfare of young animals such as rats and dogs, it does not follow that they are necessarily essential for human beings. The question whether unsaturated fatty acids deficiency plays a part in the pathology of the dermatoses in man is still a matter of considerable controversy. Hansen,[236] Faber and Roberts,[237] and Finnerud et al.[238] found that the degree of unsaturation of the serum lipids tends to be low in patients with dermatitis. Moreover, the dietary use of fats rich in unsaturated fatty acids exerts a beneficial effect in children with infantile dermatitis (Hansen[236]) and in certain patients with dermatitis skin eruptions (Cornbleet[239]). In cases of dermatitis with a subnormal iodine number of the fatty acids of the blood serum, Finnerud et al.[238] reported decided benefit after lard was added to the diet. Coincident with this improvement, a rise in the iodine number of the serum fatty acids was observed. However, Taub and Zakon,[240] Epstein and Glick,[241] and other authors were unable to see any clinical betterment by the use of unsaturated fatty acids. This important question needs further clarification.

Another interesting contribution was made by Pottenger.[242] He reported a thermolabile factor in fats, the therapeutic value of which is destroyed by heat processing incident to cooking and which seems to be of some importance for the treatment of such dermatoses as infantile dermatitis, keratoses, and scleroderma. Moreover, he described a peculiar bronze cast of the skin as indicative of a disturbance in fat metabolism which responds to treatment with the thermolabile fat factor. To overcome the deficiency described above, Pottenger prescribes a high protein diet

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235. WILLIAMSON, R.: Biochem. J. **35:** 1003, 1941.
236. HANSEN, A. E.: Am. J. Dis. Child. **53:** 933, 1937.
237. FABER, H. K. and ROBERTS, D. B.: J. Pediat. **6:** 490, 1935.
238. FINNERUD, C. W., KESLER, R. L., and WIESE, H. F.: Arch. Dermat. & Syph. **44:** 849, 1941.
239. CORNBLEET, T.: Arch. Dermat. & Syph. **31:** 224, 1935.
240. TAUB, S. J. and ZAKON, S. J.: J. A. M. A. **105:** 1675, 1935.
241. EPSTEIN, N. N. and GLICK, D.: Arch. Dermat. & Syph. **35:** 427, 1937.
242. POTTENGER, F. M., JR.: South. M. J. **37:** 211, 1944.

and a daily ration of 3 ounces of raw brain and 1½ to 3 ounces of raw liver. The thermolabile factor has also been found to be especially abundant in solvent processed, low heated soy bean lecithin, of which Pottenger gives 6 to 10 grams daily. This preparation has the additional advantage of being more palatable.

While high fat diets ostensibly have a deleterious influence in certain skin diseases such as xanthoma and psoriasis, they do not affect cutaneous infections, as shown in experimental animals by Pillsbury and Sternberg[163] and confirmed by Callaway and Noojin.[243]

Especially interesting is the question as to the influence which either a high fat or low fat diet may have on the carbohydrates of the blood and of the tissues. With regard to a diet high in fat, Adlersberg and Porges[244] have pointed out that in diabetics this kind of diet seriously disturbs the capacity to assimilate carbohydrates and markedly lowers the sugar tolerance. Stolte,[245] as well as Hirsch-Kauffmann and Knauer,[246] has demonstrated that a high fat intake creates a frank hyperglycemia in diabetics and nondiabetics alike. Even in normal individuals a high fat diet results in a liver poor in glycogen (Lusk,[247] Guest[248]). According to Himsworth,[212] both men and animals kept on a diet high in fat present a more prolonged and far more pronounced hyperglycemia following glucose administration, than do subjects on a diet high in carbohydrates.

In experiments on rabbits, Urbach and Lentz[248a] studied the effect of high fat diet by administering 2 cc. of cottonseed oil or cod liver oil to fasting rabbits previously on a normal diet, and found that it produces a progressive decrease in the skin sugar amounting to more than 10 per cent after three hours, while at the same time the blood sugar showed a slight tendency to increase. This trend is even more pronounced when animals are fed these oils daily for one week. The fasting skin sugar of rabbits so prepared shows a drop of about 23 per cent while the blood sugar is practically unchanged.

We studied also the influence of a low fat diet on the fasting blood sugar and skin sugar in man.[11] Individuals who adhered to the low fat regimen for five weeks showed a definitely higher blood sugar and skin sugar than when they were maintained on a low carbohydrate intake.

Our investigation explains the seemingly paradoxical findings of Wile, Eckstein, and Curtis,[249] who noted involution of xanthoma in patients on a diet low in carbohydrates and relatively high in fats while the lipemia

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243. Callaway, J. L. and Noojin, R. O.: J. Invest. Dermat. 3: 71, 1940.
244. Adlersberg, D. and Porges, O.: Med. Klin. 27: 1783, 1931.
245. Stolte, K.: Med. Klin. 29: 288, 1933.
246. Hirsch-Kauffmann, H. and Knauer, H.: Med. Klin. 29: 562, 1933.
247. Lusk, G.: The Science of Nutrition. Philadelphia: Saunders, 1928.
248. Guest, M. M.: J. Nutrition 22: 205, 1941.
248a. Urbach, E., and Lentz, J.: J. Invest. Dermat. in press.
249. Wile, U. J., Eckstein, H. C., and Curtis, A. C.: Arch. Dermat. & Syph. 19: 35, 1929.

increased and the tumors became more numerous when the amount of sugar in the diet was raised.

A low fat regimen is particularly valuable in the treatment of lipoid diseases of the skin. This form of dietary may be employed in three different ways: (1) A diet excluding all animal fats (milk, milk products, meat, poultry, eggs, entrails) but permitting vegetable fat, such as olive oil and pure vegetable margarine. This diet, which was introduced by Schoenheimer[120] and by Thannhauser,[121] is based on the fact that plant sterols cannot be absorbed by the human organism, and consequently lead to an appreciable decline in the serum cholesterol. On this diet carotene must be taken, lest symptoms of vitamin A deficiency make their appearance. (2) A diet free of cholesterol and low in fats, to which lecithin (Adlersberg and Sobotka[123]) or wheat germ oil (Combes[250]) is added. Kesten and Silbowitz[122] and other investigators have shown that soya lecithin, fed to rabbits receiving cholesterol, restricts hypercholesterinemia and diminishes the incidence of experimental arteriosclerosis. (3) A diet free of vegetable fat and very low in animal fat (Tables 26 and 27), with the addition of lecithin. This combination has proved very effective in our hands in the treatment of xanthelasmatosis, particularly when fortified with generous amounts of soy bean lecithin (50 Gm. daily) over a period of many weeks (p. 542).

During the past ten years the use of low fat diets (Tables 28, 29) in psoriasis (introduced by Gruetz[251]) has attracted considerable attention. While this form of diet has unquestionably proved to be beneficial (Figs. 32, 32a), notably in obese individuals, Gruetz's assumption that psoriasis is fundamentally due to a generalized disturbance of the fat metabolism has been rejected by the great majority of observers (Madden,[252] LeWinn and Zugerman,[253] Urbach[254]). The present writer, as well as Cornbleet,[255] believes that the favorable results of low fat diets in psoriasis are to be attributed to the subsequent state of undernourishment which influences the tissue metabolism (see Psoriasis, p. 443).

Sutton, Jr.,[256] regards acne vulgaris as a pustular lipoidosis and has reported good results with low fat diets and thyroid medication. We are also of the opinion that fat should be restricted in the dietary treatment of acne, but we feel that the interpretation of this disease as a manifestation of a disturbance of the low fat metabolism is highly debatable. (For a full discussion see p. 489.)

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250. Combes, F. C.: Arch. Dermt. & Syph. **49:** 144, 1944.
251. Gruetz, O.: Arch. f. Dermat. u. Syph. **170:** 143, 1934.
252. Madden, J. F.: Arch. Dermat. & Syph. **39:** 268, 1939.
253. LeWinn, E. B. and Zugerman, I.: Am. J. M. Sc. **201:** 703, 1941.
254. Urbach, E.: Delib. 9th Internat. Dermat. Congress **2:** 657, 1936.
255. Cornbleet, T.: J. Invest. Dermat. **4:** 451, 1941.
256. Sutton, R. L., Jr.: South. Med. J. **34:** 1071, 1941

The observation that seborrheic dermatitides show improvement on low fat diets is interesting and significant. Some thirty years ago Montgomery[257] called attention to the fact that an excess of fat, particularly of milk fat (cream, butter), induces the sebaceous glands to secrete lipids which are

Table 26.—*Fat-free Diet**

Purpose of the diet: Lowering of the lipid level of the blood and of the cutaneous fat deposits in lipoid diseases of the skin.

The following foods are prohibited:

All meats except lean beef
All poultry
All fish and fish roe
Egg yolk
Milk
Cream
Butter
Ice cream
All cheese except plain cottage cheese
Margarine
All shortenings, both animal and vegetable
Shortened foods such as pie crusts, cake, biscuits
All fried foods
All vegetable oils
Soups

Gravies
Peanut butter
Nuts
Chocolate
Cocoa
Cod liver oil
Vitamin concentrates

Corn
Bananas

The following foods are permitted:

Lean beef once daily
White of egg
Plain cottage cheese
Bread
Cereals

All fruits except bananas
All vegetables except corn
Gelatin
Tapioca
Sugar
Jelly
Preserves
Marmalade
Syrups
Molasses
Candies made of sugar but not of butter, nuts, spices
Salt, pepper, spices

* The amount of fat in the single daily serving of boiled lean beef is so small that the diet can, for all practical purposes, be considered fat-free.

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[257] Montgomery, D. W.: J. Cutan. Dis. 34: 829, 1916.

especially liable to bacterial action, whereas these glands normally secrete a fatty substance largely composed of cholesterol esters which are very resistant to bacteria.

Barber[179] and the Suttons[258] pointed out that excessive consumption of fats aggravates seborrheic conditions in adults. According to Finkelstein,[259] seborrheic dermatitis in children is primarily a disturbance of fat and protein metabolism, resulting in dyskeratosis with secondary inflammation. He therefore recommends a diet poor in fat and relatively rich in protein (for details see p. 402). Freudenberg and Schornstein,[260] Redaelli,[261] and other investigators have confirmed the beneficial effect of low lipoid diets in the seborrheic forms of infantile dermatitis. Figures 141, 142 on p. 385 show the gratifying results the present writer has obtained in the treatment of this dermatosis, as well as in other infantile dermatitides, through the use of such diets.

TABLE 27.—*Sample Menu for a Fat-free Diet*

Breakfast	Orange juice Toast with marmalade Tea with sugar but without milk or cream
Luncheon	Cooked vegetables, 200 to 250 Gm. (6 to 8 oz.). These may be flavored with nutmeg, celery, leeks, onions, or similar agents Bread Salad prepared with sugar and lemon juice Tea with sugar only
Dinner	Lean boiled beef Boiled potato, carrots Salad prepared with crushed pineapple and cottage cheese Bread or toast with jelly Stewed fruit Tea with sugar only

Because of the low calcium content of the diet 15 Gm. (½ oz.) of calcium gluconate should be given three times daily.

The question of low fat diets in cutaneous diseases due to underlying liver or gallbladder disturbances is discussed in some detail on p. 332.

We must not fail to stress here the point that it is essential to observe the various diets very strictly for months at a time in order to deal effec-

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258. Sutton, R. L. and Sutton, R. L., Jr.: J. Invest. Dermat. 3: 152, 1940.
259. Finkelstein, H.: Am. J. Dis. Child. 54: 344, 1937.
260. Freudenberg, E. and Schornstein, L.: Ztschr. f. Kinderh. 57: 675, 1936.
261. Redaelli, E.: Giorn. ital. di dermat. e sif. 76: 765, 1935.

TABLE 28.—*Low Fat Diet*

Purpose of the diet: (1) The depletion of pathologic accumulations of lipids in the skin and other organs resulting from disturbances in fat metabolism. (2) The possible reduction of excessive sebaceous secretion when an underlying disturbance of fat metabolism is suspected. (3) The management of the dietary aspect of the treatment of pruriginous dermatoses on the basis of gallbladder disease.

The following foods are prohibited:

A. Containing animal fat:
- Fatty soups
- Gravies
- Sausage
- Bacon
- Fat meats, such as pork, mutton
- Fat poultry, such as turkey, duck, goose, fat chicken
- Fat fish, such as herring, carp, mackerel, salmon, eels, sardines in oil, tuna
- Fish roe
- Egg yolk
- Cheeses, except cottage cheese
- Shortenings, including butter, lard, rendered fats
- Whole milk or buttermilk
- Cream
- Cakes, pastries, cookies, ice cream
- Cod liver oil

B. Containing vegetable fat:
- Olives
- Soy beans
- Bananas
- Avocados
- Nuts
- Cocoa and chocolate
- Vegetable shortenings, margarine
- Vegetable oils, including olive, peanut, corn, cottonseed
- Mayonnaise and oily salad dressings

All fried foods

The following foods are permitted:

- Soups made of lean beef and skimmed of of fat after chilling
- Lean beef, roast, boiled, broiled
- Lean veal
- Lean game, including hare, venison
- Lean ham, smoked
- Lean fowl, including squab, chicken, pheasant, partridge
- Fish, such as pike, pickerel, shellfish
- Skim milk, 250 cc. (6 oz.) daily
- All fruits and berries except banana and avocado
- Flour and cereal grains (wheat, rice, barley, oat, buckwheat)
- Noodles, macaroni
- Breadstuffs (wheat, rye), zwieback, toast, rolls
- Sugar, malt, honey, syrups, molasses
- Marmalade, jelly, jam, preserves
- Candies free of chocolate and nuts
- Coffee
- Tea

tively with the disturbed fat metabolism. Improvement can be recognized by regression of the skin manifestations (for example, xanthoma nodules) and by a decline in the blood cholesterol level.

TABLE 29.—*Sample Menu for the Low Fat Diet*

Breakfast	
Fruit	orange juice
Cereal	farina with skim milk
Bread	toast with strawberry preserves
Beverage	coffee ⅔ with hot skim milk ⅓ and sugar
Lunch	
Fruit	tomato juice
Salad	lettuce with grated pineapple, grated carrot, cottage cheese
Bread	rolls with grape jam
Beverage	tea, sugar, lemon slice
Dessert	baked apple
Dinner	
Fruit	apricot juice
Soup	tomato bouillon with rice
Meat	roast lamb
Vegetables	fresh Lima beans, turnips,
Bread	whole wheat bread, mint jelly or orange marmalade
Beverage	coffee or tea as for breakfast or lunch
Dessert	cornstarch pudding

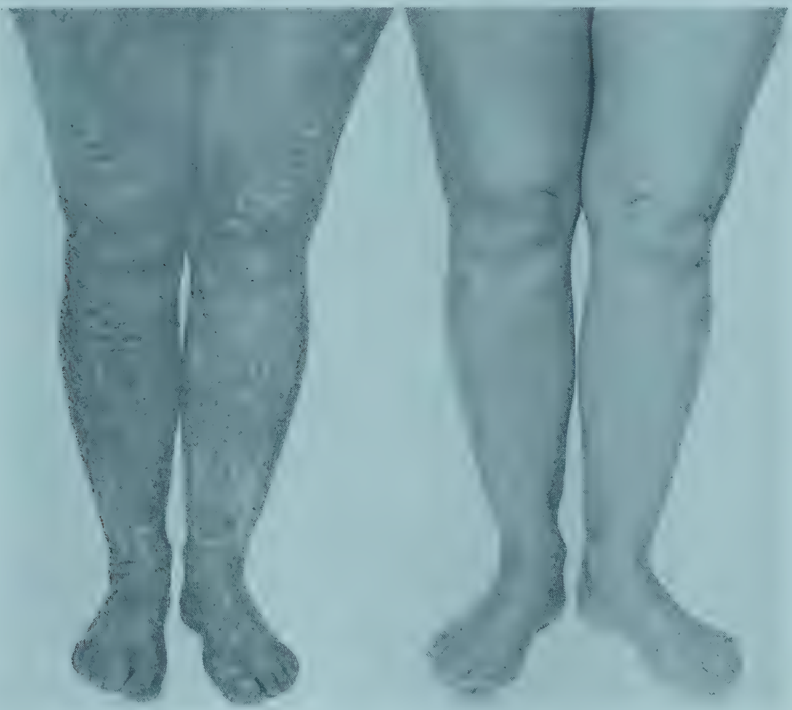

FIG. 32 FIG. 32a

INFLUENCE OF A LOW FAT DIET ON PSORIASIS VULGARIS

FIG. 32. Before dietary treatment.

FIG. 32a. After eight weeks of a low fat diet.

F. LOW PROTEIN DIET

The relations between food protein and the physiology and pathology of the skin are discussed in some detail in the section entitled "High Protein Diet." Here we shall consider only the damage that excessive protein consumption may cause in certain skin conditions as well as in healthy individuals.

The question of the influence of various dietaries on the blood vessels of the skin was examined by Gaensslen[262] in a series of histologic studies. His observations are of fundamental importance. He reports that in individuals long on a meat diet, the capillaries are markedly enlarged and the peripheral vessels contain an abnormal abundance of blood. The ruddy "butcher's face" is cited as a clinical example. This condition often leads to capillary tortuosities and aneurysms which may ultimately result in hemorrhage. On a vegetable diet the excessive peripheral blood supply recedes, the capillaries themselves straighten out, and the tortuosities disappear.

On the basis of clinical observations, Gerson[263] has arrived at the conclusion that the less protein in the diet the more rapid the regression of cutaneous inflammations, whether of tuberculous or nontuberculous origin. Furthermore, this author stresses the effects of a high protein diet on patients prone to vascular spasm. For these reasons Gerson emphasizes the importance of keeping patients with skin tuberculosis on a low protein diet (p. 66). It must be noted, however, that the Sauerbruch-Herrmannsdorfer diet, which has been found to be just as effective as the Gerson diet in cases of lupus, is relatively high in protein. However, since low protein diets and low sodium chloride diets are similar in their influence on inflammatory processes in the skin and since both the Gerson diet and the Sauerbruch-Herrmannsdorfer diet call for a drastic restriction of table salt, the gratifying results obtained with the latter diet do not admit of any conclusions as to the influence of protein restriction.

A relationship between the amount of protein in the diet and the degree of anaphylactic hypersensitiveness was noted by Ballestero.[264] He reported that limitation of ingested proteins to 10 per cent of the total caloric value (approximately 60 grams of protein in thirty days) markedly decreases the anaphylactic response in animals; however, a high protein diet does not seem to increase the hypersensitiveness.

According to Bulkley[5] and Schamberg,[265] the outstanding indication for a low protein diet (Table 30) is psoriasis. While Bulkley deserves credit for recognizing the influence of a low protein diet on the course of psoriasis, it was Schamberg and his associates[266] who most thoroughly investigated this question in a series of painstaking metabolic studies. On the basis of this work he stated that a low protein diet alone, without any other internal or external treatment, is capable of clearing up the greater part of a psoriatic eruption, particularly in cases presenting widespread lesions (Figs. 33, 34). Conversely, a high nitrogen diet exerts an unfavorable influence on psoriasis, commonly causing an extension of the eruption. While Schamberg does not claim that nitrogenous food is the cause of psoriasis or that this dietary approch is a cure for the disease, he does contend that the low protein diet so alters the terrain that the eruptions become quiescent, in which state the skin tolerates medication which was previously irritating and therefore of no therapeutic value.

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[262] Gaensslen, M.: Klin. Wchnschr. 6: 786, 1927.

[263] Gerson, M.: Wien. Klin. Wchnschr. 48: 847, 1935.

[264] Ballestero, L. H.: Rev. Soc. argent. de biol. 19: 10, 1943.

[265] Schamberg, J. F.: J. A. M. A. 98: 1633, 1932.

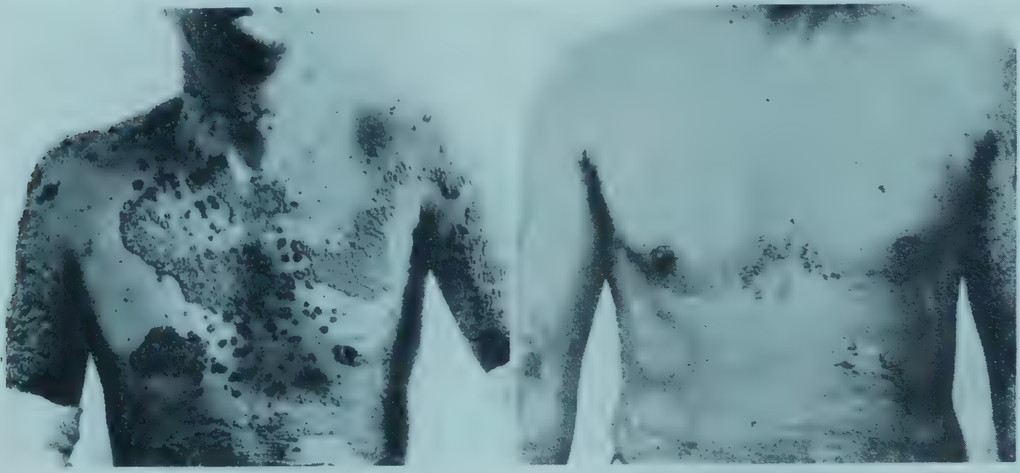

Fig. 33 Fig. 34

Influence of a Low Protein Diet on Psoriasis Vulgaris

Fig. 33. Before dietary treatment.

Fig. 34. After ten weeks on a low protein diet, with no other internal treatment or local therapy except the occasional use of vaseline.

Schamberg explains the action of the low protein diet in the following manner. In psoriasis there is rapid growth, proliferation, and exfoliation of epidermal cells. For this process these cells require building material which can be obtained only from the blood and the lymph. The principal building material required by these cells is protein. The velocity of their growth is directly proportionate to the amount of nitrogenous substances placed at their disposal. Thus, a high protein diet is prone to stimulate the growth of these cells. By keeping the patient on a low protein diet, allowing just enough protein to meet the body's wear and tear requirements, a condition is brought about in which no surplus protein is available for the rapid multiplication of the cells of the skin.

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[266] Schamberg, J. F., Kolmer, J. A., Ringer, A. J., and Raiziss, G. W.: J. Cutan. Dis. 31: 698, 1913

Schamberg was able to demonstrate that patients with very extensive psoriasis lose large amounts of nitrogen in the exfoliated cells, which consist of almost pure protein. It is quite obvious, therefore, that the excessively exfoliating skin in psoriasis requires great quantities of nitrogen and that restriction of nitrogen ingestion will serve to inhibit the pathologic proliferation of the cells (Rothman and Schaaf[41]). This view has been supported by experimental studies. Voeltz[267] found that adult merino sheep, weighing some 30 Kg., need approximately 0.7 Gm. of nitrogen daily for the growth of their wool and approximately 0.1 Gm. of nitrogen daily for other epidermal appendages such as hoofs and horns. Scheunert et al.[268] gave an adult ram such an extremely low protein diet that a depletion of the body protein—or, in other words, a negative nitrogen balance—would certainly have resulted if the animal had required as much as 0.8 Gm. of nitrogen daily for the growth of the fur and other epidermal appendages. However, the nitrogen balance was undisturbed; but at the end of 116 days it was observed that the animal, which had been shorn before the experiment was begun, had a strikingly sparse and short growth of wool. These data show that the minimal quantities of protein required to maintain life do not always suffice to supply the skin with material necessary for growth of wool, horns, and hoofs, and that a protein deficiency can lead to disturbances in the formation of these structures.

Schamberg gives a strict low protein diet (4 to 5 Gm. a day) for one week. He recommends that the patients be hospitalized, since the food must be weighed and the diet must be carefully supervised as to both quantity and quality. Table 31 gives a sample menu for a low protein diet.

Gratifying results with a low protein diet in the treatment of psoriasis have also been reported by Becker and Obermayer,[269] Brundage,[270] Schiff,[271] Stokes,[272] and Strickler.[273] Fox,[3] Brocq,[274] and Ito[275] have observed exacerbation of psoriasis lesions following ingestion of large quantities of meat. However, there is almost unanimous agreement that in most cases there is no necessity for restricting the diet as rigidly as originally prescribed by Schamberg. Most authors feel that it is sufficient to eliminate all meat, fowl, and fish and to restrict other animal protein as well as those vegetables that have a relatively high nitrogen content, such as peas, beans, lentils, and nuts.

267. Voeltz, W.: Biochem. Ztschr. **102:** 150, 1920.
268. Scheunert, A., Klein, W. and Steuber, M.: Biochem. Ztschr. **133:** 137, 1922.
269. Becker, S. W. and Obermayer, M. E.: Modern Dermatology and Syphilology. Philadelphia: Lippincott, 1940.
270. Brundage, C. L.: J. Oklahoma M. A. **22:** 407, 1929.
271. Schiff, E.: Jahrb. f. Kinderh. **145:** 299, 1935.
272. Stokes, J. H.: personal communication.
273. Strickler, A.: New York State J. Med. **104:** 506, 1916.
274. Brocq, L.: Ann. de dermat. et syph. **1:** 156, 1910.
275. Ito, M.: Jap. J. Dermat. and Urol. **39:** 80, 1936

In the chapter on psoriasis we shall show that the low nitrogen intake probably only one of the many factors which cause the eruption to d appear. Moreover, the chief drawback of this diet is that the patien

TABLE 30. *Low Protein Diet*

Purpose of the diet: Reduction of the nitrogen intake to levels just adequate meet the wear and tear requirements of the body.

The following foods are prohibited:
Lean meats
Liver, kidney, sweetbread, spleen, heart, lung
Poultry
Fish, fish roe, lobster, crab, and other crustaceans
Game
Eggs
Cheese
Dried peas, beans, and lentils
Oatmeal and wheat cereals
Soy beans
Nuts

The following foods are permitted:
Bread, rolls
Cereals
Fruits and fruit juices
Berries
Vegetables, including:
  cabbage
  broccoli
  lettuce
  carrots
  string beans
  white potato
  rhubarb
  turnips
  celery
  onion
  Brussels sprouts
  cauliflower
  parsley
  eggplant
  okra
  sweet potato
  tomato
  squash
  corn
Butter
Shortenings, oils, mayonnaise
Olives
Jellies, jams, marmalades
Sugar, honey, syrup, molasses
Cornstarch, tapioca

are very hungry and that there are bound to be recurrences of the sk eruption sooner or later when a normal diet is resumed.

In cases of severe or generalized psoriasis, Bulkley[4] prescribes a die consisting only of boiled rice, bread, butter, and water, three times a day for five days. On the sixth day the patient is permitted to return to a mixed diet gradually, a moderate meal being taken at noon and the rice continued morning and night. If all goes well, a light breakfast is given the next day, the rice diet being continued for the evening meal. The rice should be thoroughly cooked, for half an hour or so, with water and not with milk, and then left uncovered on the fire to dry out. It is to be

TABLE 31.—*Sample Menu for Low Protein Diet (Schamberg[illegible])*

Food	Amount Gm.	Nitrogen Per cent	Nitrogen Gm.	Calories
Breakfast				
Bread	20	1.55	0.31	53
Butter	15	0.12	0.02	113
Grape nuts	10	1.96	0.20	40
Orange	180	0.128	0.23	83
Apple	135	0.064	0.09	77
Tea	125	0.015	0.02	
Cream	30	0.36	0.10	57
Total			0.97	423
Lunch				
Bread	15	1.55	0.23	39
Butter	15	0.12	0.02	113
Grapes	150	0.208	0.31	129
Lima beans	50	1.21	0.60	37
Turnips	75	0.118	0.09	31
Cornstarch	189	0.065	0.12	297
Potato cake	300	0.275	0.82	273
Tea	125	0.015	0.02	
Total			2.21	919
Supper				
Bread	25	1.55	0.39	66
Butter	15	0.12	0.02	113
Prunes	88	0.08	0.07	63
Cauliflower	75	0.336	0.25	22
Corn	100	0.368	0.37	85
Celery	25	0.176	0.04	5
Potatoes	200	0.255	0.51	182
Total			1.69	536
Total for day			4.87	1,878

served with an abundance of butter and little salt, and to be eaten very slowly with a fork. It should be thoroughly masticated, in order to secure the full action of the saliva. The patient should spend at least a half hour over this simple meal. The bread should be at least twenty four hours old, well buttered, and it should be very thoroughly chewed, or fletcherized. Water, hot or cold (not iced), is to be taken freely, but not together with the food.

Incidentally, Bulkley also recommends the low nitrogen diet for acute inflammatory eruptions of the skin, and particularly for acute dermatitis.

G. LOW URIC ACID DIET

A review of the literature (helpfully summarized by Lutz[276]) concerning the connection between various dermatoses and a gouty diathesis reveals the fact that only one skin condition, the gouty tophus, can at present be regarded as specifically of gouty origin. Some authors—Kromayer,[277] for example—have attributed many cases of dermatitis, pruritus, and psoriasis to an underlying disturbance in uric acid metabolism, basing their assumption on certain cutaneous manifestations in association with elevated uric acid levels in the blood or urine, but without the presence of the characteristic features of gout. Such claims must be peremptorily rejected. High fasting uric acid levels in the blood and tissues are by no means necessarily an indication of a gouty condition. For, as the writer has shown in man and in animals,[135] the uric acid content of the blood and tissues can be arbitrarily increased by any nonspecific irritation of the skin. It is true that in many widespread dermatoses—especially in those in which leukocytosis and unusual destruction of cells occur, as in extensive dermatitis, psoriasis, or Hodgkin's disease—the uric acid in the blood and skin is found to be high. However, when under suitable treatment the dermatosis clears up and the level of the uric acid falls, the previous increase in uric acid must be regarded not as the cause but as the result of the dermatosis in question (Whitfield[217]). Graf[278] determined the blood uric acid level in 150 cases with cutaneous manifestations. While it was elevated and subsequently restored to normal by cinchophen in 22 per cent, only in 2 of these cases was the decrease of the uric acid followed by clinical improvement of the dermatosis. He disputes, therefore, the etiologic importance of the hyperuricemia found in skin diseases.

A given dermatosis cannot be regarded as an expression of an underlying uratic diathesis unless (1) a uric acid tolerance test (with phenylchinoline carbonic acid, Midana[279]) reveals the delayed uric acid elimination so characteristic of gout, accompanied by an increase in the uric acid content of the blood and a simultaneous eruption or exacerbation of skin lesions and (2) the given dermatosis yields to a purin-free diet or to treatment with cinchophen, or colchicum, without any external medication.

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[276] Lutz, W.: Stoffwechsel und Haut, in Handbuch für Haut und Geschlechtskrankheiten, vol. iii, 1929.

[277] Kromayer, E.: Deutsche med. Wchnschr. **51:** 112, 1925.

[278] Graf, H.: Arch. f. Dermat. u. Syph. **162:** 726, 1931.

[279] Midana, A. and Peruccio, L.: Giorn. ital. di dermat. e sif. **78:** 201, 1937.

However, the literature does contain reports of occasional cases in which there seems to be a direct connection between the presenting dermatosis and gout. Thus Lesser,[280] as well as the present writer, has seen severe urticarial eruptions make their appearance during attacks of gout.

Spiegler and Grosz,[281] Waelsch,[282] Foucault,[283] Scholz,[284] and other dermatologists have reported isolated cases of dermatitis which had been refractory to all types of local treatment for years, and which finally yielded promptly to a strict gout diet. Urticaria with a crusted papular rash of three years' duration in a patient with abnormally high concentration of uric acid in the blood was reported by Comel[285] as prurigo uratica, because it was relieved by adherence to a low purine diet.

Volar erythema, involving particularly the lateral aspects of the palms and soles along with hyperkeratosis at the pressure areas, was noted by Barber[286] as a gouty manifestation, improved by antigout therapy. Schmidt and Wohlstein[287] describe an attack of gout in which the patient developed a sharply circumscribed reddening and regional edema of the leg, accompanied by chills and fever. During the attack the uric acid level in the blood was 1.9 mg. per cent as compared with 9.6 per cent during periods of latency, evidently due to retention of uric acid in the cutaneous tissues. Moreover, it is well known that gouty individuals suffer severe generalized and local itching, especially before the onset of an attack.

J. Jadassohn[220] is of the opinion that gout, being a constitutional disease, may alter the cutaneous suceptibility to external dermatitis-causing agents. In this connection he refers to Ehrmann's observation[288] that the skin of gouty individuals shows unusually strong reactions to external application of relatively mild skin irritants such as tar or chrysarobin, and also to internal iodine treatment. It is possible, therefore, that the temporary rise in the uric acid level in the blood (so-called uratohistechia), together with inadequate uric acid excretion, is responsible for an alteration in the reactivity of the skin with the result that external agents can cause dermatoses of various types.

Once the diagnosis of gout has been unequivocally established, the consumption of all foods which may be a source of uric acid—in other words,

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280. Lesser: Dermat. Ztschr. **11:** 423, 1904.
281. Spiegler, E. and Grosz, S.: in Mracek: Handb. d. Hautkr. **1:** 267, 1902.
282. Waelsch, L.: Prager med. Wchnschr. **30:** 591, 1905.
283. Foucault: Dermat. Wchnschr. **40:** 526, 1905.
284. Scholtz, M. W.: Die innere Behandlung d. Hautkrankheiten. vol. viii. Halle: Marhold, 1925.
285. Comel, M.: Dermat. Ztschr. **78:** 73, 1938.
286. Barber, H. W., Hunt, E., Pringle, G. L. K., and Yeoman, W.: Proc. Roy. Soc. Med. **31:** 701, 1938.
287. Schmidt, L. and Wohlstein, E.: Münch. med. Wchnschr. **78:** 574, 1931.
288. Ehrmann, S.: Arch. f. Dermat. u. Syph. **138:** 346, 1922.

purine-containing foods—must be avoided. Even after the acute symptoms have been controlled and the patient is again allowed to partake of limited amounts of foods containing purines, all of the highly cellular internal organs must be prohibited. Moreover, the intake of meat and fish must be restricted to some 150 Gm. (6 oz.) two or three times weekly. It should be mentioned in this connection that it is immaterial whether the meat is "white" or "dark." But there is definitely a difference between boiled and fried meats; the latter are to be strictly forbidden. When meat is boiled some of the cellular substances are dissolved by and discarded with the water, which is the reason why meat broths and soups must be prohibited. Recent experience in the treatment of gout indicates that a restriction in the fat intake is desirable.

TABLE 32.—*Dietary Treatment of Gout*

Purpose of the diet: To restrict the intake of purine-containing foods in accordance with the ability of the organism to metabolize them.

The following foods are prohibited:

Glandular organs, including brains, kidney, sweetbreads, liver, heart
Meats of all types
Meat extracts
Gravies, broths, and soups made from or with meat
Fish, oysters, crustacea, roe
Poultry
Game

Asparagus
Eggplant
Peas, fresh or dried
Beans, Lima or string, fresh or dried
Lentils
Spinach
Mushrooms

Tea
Coffee

Yeast

The following foods are permitted:

Milk and buttermilk
Cream
Butter
Cheese

Eggs

All cereal grains
Bread and rolls
Macaroni, spaghetti, noodles
Cakes
Tapioca
Sago

All vegetables, except as noted

All fruits and berries

Almonds
Hazelnuts
Walnuts

Sugar
Syrup
Molasses
Honey

Olives
Decaffeinized coffee or coffee substitute
Cocoa
Chocolate

Gelatin

The influence of alcohol in gout is detrimental and its use should be discouraged. Although the nature of the diet in the treatment of gouty diathesis removes or restricts some of the best sources of the vitamin B complex, namely meats and glandular organs, it is unwise to replace them with yeast, since this contains nucleic acid, which is a source of uric acid.

H. LOW POTASSIUM DIET

Incedayi and Ottenstein[289, 290] were the first to prescribe a low potassium diet in combination with adrenal cortical extract or ascorbic acid for treating psoriasis. This dietary approach was suggested by the familiar fact that injections of large doses of sodium chloride are very beneficial in treating the characteristic crises of Addison's disease, since the loss of sodium and chlorine constitutes one of the disturbances in this disease which brings on crises. Moreover, Kendall, Harrop, and other investigators found that the sodium ion is even more necessary than the chloride ion for preventing these crises, and therefore administered massive doses of sodium bicarbonate or sodium citrate. However, studies on animals showed that the results obtained with sodium salt therapy alone were not so good as those obtained with salt plus cortical extract. Kendall

TABLE 33.—*Sample Menu for a Case of Severe Gout*

Breakfast	
Fruit	stewed plums
Cereal	oatmeal with cream and sugar
Egg	one egg scrambled with cottage cheese
Bread	toast or rolls with marmalade or preserves
Beverage	milk or cocoa
Lunch	
Platter	steamed rice with tomato sauce, beet greens, buttered squash, broccoli
Bread	bread or muffins with butter
Dessert	sponge cake with canned apricots
Beverage	decaffeinized coffee or coffee substitute with cream and sugar; or milk
Dinner	
Soup	cream of celery soup
Platter	2 deviled eggs, baked potato, beets
Salad	lettuce with dressing of olive oil and lemon juice
Bread	bread or rolls with butter
Dessert	fresh fruit cup
Beverage	as for lunch

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289. INCEDAYI, C. K. and OTTENSTEIN, B.: Dermatologica **80:** 65, 1939.
290. INCEDAYI, C. K. and OTTENSTEIN, B.: Dermatologica **84:** 330, 1941.

and Harrop also observed that a diet extraordinarily low in potassium served to keep alive adrenalectomized animals which were given sodium chloride and sodium citrate at the same time. The effect of this diet was to equilibrate the level of the electrolytes in the blood, for immediately after the operation the blood sodium level showed a decline and the potassium level a rise, just as in Addison's disease. On a low potassium diet without cortical extract these animals were so sensitive to small quantities of potassium that even 0.5 Gm. of potassium could evoke a crisis which was equivalent to acute adrenal insufficiency.

The beneficial effects of a low potassium diet in adrenal gland disturbances are thus fully explained by these experiments, in which it has been shown that (1) increased potassium intake provokes crises in adrenalectomized animals, and (2) decreased potassium intake can lower the requirements for sodium chloride and for cortical extract. It is also known, moreover, that under the influence of diet the mineral balance of the skin may be changed, the potassium showing an increase over the calcium (see p. 26).

These facts induced Incedayi and Ottenstein[289] to prescribe a low potassium diet and adrenal cortical extract for psoriasis patients, since according to Grueneberg[291] in this disease there is a disturbance of the adrenal cortical function. Incedayi and Ottenstein have reported highly gratifying results with this method. Furthermore, because of the recent emphasis on the connection between ascorbic acid and the adrenal cortex these authors[290] have treated cases of psoriasis, in which the urinary vitamin C excretion was reduced, with adrenal cortex therapy in the form of a low potassium diet together with large doses of vitamin C. Again they reported very satisfactory findings. Administration of vitamin C alone, however, was of no apparent value. These Turkish investigators do not claim that this therapy is specific for psoriasis but that it stimulates general cellular metabolism and especially the adrenal cortex itself. They suggest that a combination of vitamin C, adrenal cortex extract, and a low potassium diet might produce even more striking results. However, the present writer together with LeWinn[292] tried these combined agents on a group of 18 psoriasis cases, and failed to observe any encouraging results.

The preparation of an appetizing meal, which is to contain no more than 1.6 Gm. of potassium, requires as much skill and care as does the preparation of food for a diabetic patient. By thoroughly boiling vegetables two or three times (in fresh water each time), some 70 to 80 per cent of their salts, including potassium salts, can be removed. Thus, potatoes, for example, which normally contain more than 400 mg. per cent of potas-

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291. Grueneberg, T.: Arch. f. Dermat. u. Syph. **168:** 183, 1933.
292. LeWinn, E. B. and Urbach, E.: Arch. Dermat. & Syph. **51:** 398, 1945.

TABLE 34.—*Low Potassium Diet*

Purpose of the diet: To intensify the action of the adrenal cortical hormone, which, according to some authors, has a beneficial effect on psoriasis.

The following foods are prohibited:

Meats
Meat extracts
Caviar
Fish
Poultry

Banana
Pineapple
Rhubarb
Dried fruits, including currants, figs, dates, peaches, prunes, raisins

Honey

Beans
Lentils
Cow peas
Lima beans
Beets
Brussels sprouts
Celery
Swiss chard
Parsnips
Spinach
Dandelion greens
Potatoes
Endive
Kohlrabi
Lettuce
Mushrooms
Pumpkin
Winter squash

Wheat bran
Whole cereal grains

Chestnuts
Coconut
Hazelnut
Peanut
Pecan
Walnut

Cocoa
Chocolate
Coffee

Mustard
Paprika
Black pepper
Horse-radish

The following foods are permitted:

Cheese
Milk
Butter
Bacon
Eggs
Cream

Oysters
Clams

Bread, except whole grain breads
Crackers
Cereals, except whole grain cereals
Macaroni, noodles
Polished rice

Sugar
Maple syrup

Okra
Asparagus
Cucumber
Eggplant
Green peppers
Leeks
Onions
Summer squash
Corn
Cabbage
Tomato
Carrot
Water cress
Cauliflower
Fresh peas
Radishes
String beans

Tea

Pomegranate
Watermelon
Canteloupe
Apricots, fresh or canned
Peaches, fresh or canned
Cherries
Plums, fresh or canned
Pears
Grapes
Apples
Citrus fruits
Fruit juices

All berries, either fresh or as jams or preserves

sium, can be rendered low in potassium in this fashion and made palatable by adding table salt. The following foods contain more than 300 mg. of potassium per 100 Gm.: meat, poultry, fish of all sorts, potatoes, sweet potatoes, peas, beans, turnips, cabbage, celery, artichoke, chestnuts, spinach and other green vegetables, pumpkin, parsnip, dried fruits (particularly dates, figs, prunes), bananas, pineapple, nuts of all sorts, wheat, bran, molasses. Needless to say, all of these food items must be sharply restricted if the total intake of potassium is not to exceed 1.6 Gm. daily.

TABLE 35.—*Sample Menu for the Low Potassium Diet*
(Potassium Content between 1 and 2 Grams)

Type of Food	Example	Size of Portion	
		Grams	Household measure
Breakfast			
Fruit	orange juice	100	⅖ cup
Cereal	corn flakes with	20	1 cup
	sugar and	13	1 tablespoonful
	cream 20%	60	¼ cup
Eggs	any style		2 eggs
Bread		50	2 slices
Beverage	milk	125	½ cup
Lunch			
Platter	cheese, macaroni, carrots, stewed tomatoes; of each	60	¼ cup
Bread		25	1 slice
Butter	on vegetables and bread	20	2 pats, 1″ x 1″ x ½″
Beverage	milk (with tea, if desired)	125	½ cup
Dessert	strawberries, fresh or frozen, with	75	½ cup
	cream, 20%	30	2 tablespoonfuls
Dinner			
Eggs	any style		1 egg
	with bacon, broiled crisp	20	4 strips 7″ long
Vegetables	asparagus	100	8 6″ stalks
	corn	100	½ cup or 1 8″ ear
Bread		25	1 slice
Beverage	milk	125	½ cup
Dessert	apple sauce with	100	⅓ cup
	whipped cream	10	1 tablespoonful

Although this diet provides enough vitamins A and C, it barely provides an adequate supply of calcium and other salts or of vitamins B_1 and B_2. The lacking ingredients must, therefore, be given in the following form: calcium phosphate 0.5 Gm. (8 grains), ferrous sulfate 0.3 Gm. (5 grains), each three times daily, vitamin B complex 1 capsule three times daily.

I. LOW CALORIC DIET

Many experienced dermatologists, including G. H. Fox, L. D. Bulkley, and L. Brocq, are inclined to attribute a large proportion of all inflammatory skin diseases to the combination of excessive eating and sedentary habits. The constant overloading of the system with material which can be only partially digested and assimilated may cause many derangements of metabolism which may induce or perpetuate certain skin affections. While it is most often in regard to sweets and starches that this mistake occurs, gross errors are often made in the excessive use of foods and drinks of all kinds. A reduction of weight should therefore be advocated at the outset of treatment in every dermatologic case where the patient is overweight, because this procedure tends to increase the effectiveness of medication and local treatment.

Certain instances of adiposity are associated with endocrine disturbances. However, there is generally no reason to suspect any major alteration of metabolism involving diminished combustion. The occurrence of adiposity, even in supposedly moderate eaters, may usually be explained by the daily accumulation and storage, in the form of fat, of small amounts of food beyond maintenance requirements. In other words, this fat represents the favorable balance of intake over expenditure of matter.

Reduction of weight is of particular importance in the treatment of cutaneous conditions, such as intertriginous dermatitis, which are caused by friction between skin surfaces or by maceration subsequent to the accumulation of moisture in skin folds. Loss of weight is also indicated in such cases of dermatitis and furunculosis in infants and small children who present obesity due to overfeeding.

The proper low caloric or reducing diet consists of a restriction of the intake of calories, but in such a manner that the patient's appetite is always satisfied.

The prime objective of the reducing diet is, of course, the elimination of superfluous fat and water, while maintaining the body protein so that this regimen may be carried on for some time without disturbing the health of the patient in general, either physically or nervously. The diet should in all instances include an average of approximately 1 Gm. of protein per kilogram of body weight daily. Furthermore, it must always contain adequate quantities of minerals, vitamins, and water. When the physician plans a dietary for a given patient, he must give due consideration to the individual's living habits, daily routine, economic status, occupation, tastes, general physical characteristics, and, above all, any possible concurrent illness. The choice of reduction diet to be prescribed must depend on whether the patient is to do any physicial work during the course of the diet. No attempt should be made to hasten the weight reduction unduly; the patient should lose poundage slowly and gradually, if only because a rapid loss of fat will cause the skin, particularly of the face, neck, and breasts, to become loose and wrinkled. It is advisable to allow the patient to lose some 6 to 8 Kg. (13 to 17 lbs.) in weight during the first four to six weeks, then to increase the intake to such an extent that the patient's weight remains virtually unchanged for two months, when the diet may be adjusted to bring about an additional loss of weight.

Every reducing dietary should be preceded by measures designed to dehydrate the body or, more precisely, the skin.* This can best be achieved by an extremely low salt diet for several days before beginning the reducing regimen proper. The Karell milk diet is suitable for this purpose. When a marked degree of water retention is established, the dietary measures may be supported by injections of mercurial diuretics every two or three days. The latter may be enhanced by giving ammonium chloride (1 Gm. four times daily) for several days before and after the injection as well as on the day when the mercurial is given.

KARELL MILK DIET

Four times a day (at 8 a.m., noon, 4 p.m., and 8 p.m.) the patient takes 200 cc. of boiled milk at any temperature desired. No other liquids are given, and no solid food (with the possible exception of 3 pieces of zwieback). The milk is always to be sipped slowly, in small mouthfuls. The importance of taking the milk at regular intervals must be stressed. Complete rest in bed is absolutely essential. If the patient has an aversion to fresh milk, the diet can sometimes be carried out effectively by substituting lactic acid, Bacillus bulgaricus, or Bacillus acidophilus milk, or buttermilk or by adding some flavoring agent to the milk such as coffee, cocoa, or malt extract. In the event of constipation the patient may be given 5 to 10 Gm. of magnesium sulfate in 200 cc. of water in the morning, on an empty stomach, but no purgative mineral waters containing sodium chloride. If diarrhea occurs, the patient is to be given some type of milk processed as mentioned above. Moreover, the addition of calcium carbonate, approximately 1 gram to every 250 cc. (½ pint) of milk, may help control the diarrhea. In the event of heartburn, sodium bicarbonate or a tablespoonful of lime water may be added to the milk.

The preliminary dehydration regimen just described is followed by the reducing diet proper. This is based on the individual's standard weight in kilograms, which can be roughly calculated in adolescents and adults by subtracting 100 from the patient's height in centimeters. The daily requirement is about 30 calories per kilogram of body weight.

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* Urbach and Bauer-Jokl[293] have submitted histochemical evidence demonstrating that the skin, notably the cutis, of adipose individuals contains abnormally large quantities of water. The high water content of the skin can be readily shown by the fact that following the injection of a mercurial diuretic such as salyrgan, the patient loses 2 to 3 liters of water during the next twenty-four hours. Volhard's water excretion test may also be used to determine the presence of an excess of water in the tissues. After drinking a measured quantity of water, the patient eliminates disproportionately large quantities of urine.

293. URBACH, E. and BAUER-JOKL, M.: Klin. Wchnschr. **10:** 824, 1931.

Von Noorden[294] has listed three different degrees of therapeutic undernourishment, according to the restriction of the caloric intake:

First Degree (moderate reducing diet): Restriction of intake to four fifths of the requirements in calories, as calculated by the body weight. Thus, when 2,500 calories, for example, are indicated, the intake is restricted to 2,000 (i.e., from 30 to 24 calories per kilogram of body weight). In this form of diet the desired reduction in caloric intake is readily achieved by restricting the daily consumption of fat (chiefly in the form of butter and of fat added to various dishes) and by prohibiting sugar, candy, sweetened and carbonated beverages, and beer. In addition regular exercise is advised.

Second Degree (fairly strict reducing diet): Restriction of intake to three fifths of the estimated normal requirements. Thus, when 2,500 calories are indicated, the intake is restricted to 1,500 (i.e., 18 instead of 30 calories per kilogram of body weight). Vigorous exercise is called for here as well.

Third Degree (intensive reducing diet): The intake is restricted to two fifths of the normal requirements—1,000 calories instead of the indicated 2,500 calories (or 12 instead of 30 calories per kilogram of body weight). This regimen is so drastic that the physician must constantly be on the alert for any possible signs of cardiac complications. These are best prevented by giving, between the principal meals, small quantities of the foods which are allowed in this diet.

As pointed out above, the protein requirements must be fully met in any form of reducing diet. The nonprotein calories should be supplied principally by carbohydrates, which, since they supply bulk, are more likely to give a feeling of satiety; moreover, the protein-sparing action of the carbohydrates is greater than that of fats.

The caloric tables in Part Five will be of help to the physician in prescribing dishes which are to the individual patient's taste and still within the limits of the diet.

A reducing diet, which is distinguished by its high protein content and thus has the advantage of amply satisfying the patient's hunger, can be drawn up along the lines of Umber's "skeleton" or basic diet[295] and will contain approximately 1,000 calories. The skeleton diet is elastic and can be adjusted in accordance with the number of calories the physician prescribes in a given case.

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[294] von Noorden, C. H.: Clinical Treatises on Pathology and Therapy of Disorders of Metabolism and Nutrition. New York: Treat, 1910.

[295] Umber, F.: Ernähung, Diätküchen, Kostformen, in Handbuch f. d. ges. Krankenhauswesen. Berlin: Springer, 1930.

J. HIGH CALORIC DIET

In many cases, notably of chronic dermatitis and neurodermatitis as well as other chronic dermatoses in which the patient is considerably run down or debilitated and incapable of taking on weight, an increase in weight may be a decisive factor. In such patients, who are usually of the nervous type, general and local therapeutic measures are frequently of no avail until they have gained some 10 Kg. (22 lbs.) and thus feel decidedly better, physically and psychologically.

The fundamental principle of all fattening dietaries is not to increase the size of any particular meal or meals, but to enlarge the over-all intake by having the patient eat a greater number of meals served at intervals of two to three hours. Since meat is very satiating, it is given rather sparingly. Carbohydrates and fats (cream, whipped cream, yolk of egg) and butter play the major role in this form of diet. The gross intake should be increased gradually, and especially so in the more undernourished individuals.

When making up the exact dietary prescription for a given case, due consideration should be given to the patient's individual taste and the condition of his digestive organs. Thus, the presence of gallbladder disease may be an obstacle to a high fat intake. To achieve a gain in weight, the organism must be given at least double the normal amount of 30 calories, including the caloric value of the protein requirements. A tabulation of the nutritive values (in calories) of various foods is presented in the Appendix (Tables 98–106, pp. 574–85).

The menu given in Table 36 may serve as an example of a typical fattening regimen.

If the indicated quantities seem excessive to begin with, smaller amounts may be given at first and then rapidly increased until the desired total quantity is attained.

In many cases it is not possible to induce the patient to eat because he insists he has no appetite. In such instances the author has found Falta's treatment,[296] consisting of insulin injections in combination with high caloric diets, to be very successful.

This regimen is generally begun with 5 units of insulin given thirty minutes before breakfast, lunch, and supper. If this fails to arouse the patient's appetite, the dosage is gradually increased until 10 or even 20 units are given three times a day. The meals should be rich in carbohydrates. Readily assimilable carbohydrates must always be at hand, preferably in the form of sugar, in the event of sudden hypoglycemic reaction. In dealing with cachectic individuals, even small doses of insulin call for caution. Successful treatment is marked by a striking stimulation of the appetite, which sometimes reaches the proportions of truly ravenous hunger. This action is probably attributable to a drop in the blood sugar level due to increased glycogen formation in the liver. Much of the carbohydrate is transformed into fat and stored as such. The high fat intake, moreover, leads to a deposition of lipids in both tissue cells and fat depots. However, the total gain in weight is not to be regarded as a net gain, for insulin leads not only to a storage of fat, but also to a marked increase in the ability of the tissue cells to absorb water.

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[296] Falta, K.: Wien. klin. Wchnschr. suppl. p. 84, 1926.

As promising as the insulin–high caloric diet may appear to be, its potentialities are limited in many instances. For one thing, insulin is not effective in all cases. Furthermore, insulin loses its ability to increase body weight after a certain point in the fattening process has been reached. Insulin should be given a trial, however, in all cases in which it is found difficult to achieve a gain of weight.

TABLE 36.—*Sample Menu for a High Caloric Diet*

8 a.m.	250 cc. of milk, or—better—200 cc. (6 oz.) of table cream, with two teaspoonfuls of cocoa or coffee extract, well sweetened with sugar; 2 scrambled eggs; 1 piece of zwieback or 1 slice of buttered white bread
10 a.m.	Oatmeal with 50 to 100 Gm. (2 or 3 oz.) of butter, well sweetened with sugar; 2 sardines in oil, and toast
1 p.m.	Thick split pea soup or broth with large amount of noodles or rice; vegetables prepared with plenty of butter; 3 or 4 well cooked potatoes; pastry or ice cream
4 p.m.	1 cup of cocoa with cream, bread with plenty of butter.
6:30 p.m.	150 Gm. (5 oz.) of meat or 2 or 3 fried or scrambled eggs with sausage; 3 slices of bread and butter, 250 cc. (8 oz.) of milk
9 p.m.	200 cc. (6 oz.) of cream with cocoa or oatmeal with 30 Gm. (1 oz.) of butter or white bread with plenty of butter.

Individuals who tolerate large quantities of sugar may profitably take Depisch's "sugar breakfast"[297] to stimulate the appetite. The patient is given 50 to 100 Gm. (2 to 3 oz.) of sugar in approximately 500 cc. of tea, mornings, on an empty stomach. This is to be taken slowly (in thirty minutes or so) and not too hot. If the patient objects to the sweet taste, lemon juice or other flavoring may be added. After this "sugar breakfast" no other food should be taken for at least three or four hours. However, if the patient complains of hunger before the end of this period, he may be given orange juice or other carbohydrates. The effect of this pro-

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297. DEPISCH, F.: Wien. Arch. f. inn. Med. 13: 685, 1927.

cedure is attributable to a mild hypoglycemic reaction on the part of the organism following the intake of such an abundance of sugar—a reaction that is to be interpreted as the body's own "insulin injection," so to speak. The present writer has obtained reasonably gratifying results with Depisch's method.

K. HIGH PROTEIN DIET

Schoenheimer and associates,[127] using isotopically marked essential amino acids such as leucine and glycine, have demonstrated that skin and muscle, because they constitute so great a portion (16 per cent and 75 per cent respectively) of the total body weight, have the greatest share in the uptake of dietary nitrogen. It is not surprising, therefore, that the high protein diet has a very important place in the treatment of a variety of skin diseases characterized by hypoproteinemia resulting from depletion of plasma proteins. Such protein loss may be acute, as in extensive burns or severe pemphigus, or chronic, as in ulcers of diabetic, varicose, or decubital origin. A high protein diet is further of definite value in the management of dermatoses with unsatisfactory antibody production and those with lowered resistance to infection. Finally, skin diseases in which impaired liver function plays a role may be benefited by this type of dietary.

Protein deficiency states may be brought on by (1) insufficient intake, (2) faulty absorption or utilization, (3) excessive loss of protein, or (4) inadequacy of the mechanism which regenerates protein from amino acids.

Inadequate intake of protein-rich foods and especially of protein of high biologic value (e.g., those containing the essential amino acids) is responsible for most cases of hypoproteinemia. On page 139, we shall discuss in detail nutritional edema, also known as famine edema, hunger swelling, and prison dropsy, which is a form of protein malnutrition caused by actual lack of protein foods.

Another type of protein deficiency is presented by undernourished infants or those fed a diet which is almost exclusively made up of carbohydrates (p. 141).

Other causes of protein malnutrition are reducing diets; vegetarian regimens; elimination diets in allergic states if the suspected or known allergens are protein foods such as milk, eggs, or cereals, particularly in children whose need for protein is relatively great; poorly balanced diets maintained for long periods in diabetic patients. Moreover, an otherwise adequate protein intake may not meet the heightened requirements in thyrotoxicosis, fevers, and infections.

Faulty digestion and/or absorption occurs if the quantity of digestive juices and enzymes of the gastro-intestinal tract is substantially diminished. As a result of such a secretory deficiency the breakdown of proteins into amino acids cannot be completed, absorption likewise suffers, and hypoproteinemia ensues. This situation may be observed in achylia gastrica and in pancreatic insufficiency.

Extensive burns lead to the loss of large quantities of protein because the capillaries are damaged to such an extent that considerable amounts of protein filter out with the plasma fluid. While the plasma protein deficit following burns is an acute condition, there seems to be a chronic loss of plasma protein in certain forms of skin ulcers such as varicose, diabetic, and decubital ulcers (Altshuler and associates[298]). In decubital ulcers, plasma concentrations have been found to be subnormal (Mulholland and associates[299]); and it has been observed that oral administration of protein hydrolysate solutions is followed by a marked acceleration in the healing of ulcers due to stasis, diabetes, and decubitus (Altshuler et al.[298]). In this connection it is interesting to note Madden's animal experiments,[300] which show that nutritional plasma depletion over a period of time (twenty-five to thirty weeks) creates a tendency to skin ulceration and loss of hair in dogs.

Ravdin et al.[301] showed that in man demonstrable hypoproteinemia is associated with delayed healing of wounds. A reduction of 15 per cent in plasma protein may lead to moderate retardation, and a reduction of 25 per cent is drastic enough to cause a very serious delay or even to arrest the healing process completely. Moreover, it has been observed that a high protein intake accelerates and stimulates cellular proliferation in both injured and normal tissues (Baker and Carrel[302]).

It has recently been demonstrated that protein depletion in human beings and animals may be the direct cause of lowered resistance to infection and of inadequate antibody production. Dogs stripped of their plasma proteins and of their protein reserves by a low protein diet are very susceptible to infection and quite readily succumb to cutaneous abscesses, septicemia, and other bacterial diseases (Madden and associates[300]). Cannon[303] is the protagonist of the concept that antibody production is directly dependent upon an adequate intake of protein of high biologic value. He demonstrated that the capacity to produce agglutinins is definitely lower in rabbits made hypoproteinemic by a low protein diet than in animals of the same age which have been on a well balanced dietary. Moreover, by administering isotopic amino acids to actively immun-

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298. Altshuler, S. S., Sahyun, M., Schneider, H., and Satriano, D.: J. A. M. A. **121:** 163, 1943.
299. Mulholland, J. H., Tui, C., Wright, A. M., Vinci, V., and Shafiroff, B.: Ann. Surg. **118:** 1015, 1943.
300. Madden, S. C., Winslow, P. M., Howland, J. W., and Whipple, G. H.: J. Exper. Med. **65:** 431, 1937.
301. Johnson, J., Ravdin, I. S., Vars, H. M., and Zintel, H. A.: Arch. Surg. **40:** 1104, 1940.
302. Baker, L. E. and Carrel, A.: J. Exper. Med. **44:** 387, 1926.
303. Cannon, P. R., Chase, W. E., and Wissler, R. W.: J. Immunol. **47:** 133, 1943.

ized rats and rabbits, Schoenheimer et al.[304] showed that antibodies, like other serum and tissue proteins, participate in metabolic reactions involving the utilization of dietary nitrogen. It is now generally assumed that antibodies are specifically modified molecules of globulin. An understanding of the relationship between major protein deficiencies and increased susceptibility to infectious diseases and reduced capacity to produce antibodies is, of course, of great importance for the management of infectious skin diseases and allergic dermatoses.

Another manifestation of hypoproteinemia, one rather closely allied to the above-mentioned infectious states, concerns decreased resistance to intoxication, and seems to be mediated through the liver (Whipple[305]). The effect of protein depletion of the liver is demonstrated by the liver's increased susceptibility to hepatotoxic agents such as sulfonamides, arsphenamine, and chloroform. Low protein diets are followed by a definite fall in the protein content of the liver (Elman and Heifetz[306]). Until a few years ago it was generally believed that large glycogen stores in the liver afforded that organ maximal protection against hepatotoxic substances. However, many recent reports indicate that the importance of the carbohydrates lies in their protein-sparing property (Johnson and associates[301]). Therefore, the prevailing concept today is that a diet high in protein as well as in carbohydrates provides the best defense against such liver-damaging agents. The implications with regard to toxic skin eruptions and dermatoses in which an underlying liver disturbance is found are obvious.

Lastly, more recent investigations seem to indicate the possibility of specific amino acid deficiency syndromes, i.e., that lack of essential amino acids in the diet may cause specific changes in the human organism. Holt and associates[307] found that removal of arginine from the diet resulted in a great reduction in the number of spermatozoa in the semen. After restoration of arginine to the diet, the spermatozoa count returned to normal. These experiments, which aim primarily to discover whether deficiencies of particular amino acids can produce characteristic pathologic changes, are of potential importance for understanding the pathogenesis of certain skin diseases. There is some evidence, for example, that cystine, the sulfur-containing amino acid, may be connected with the rate of growth and the pigmentation of the hair (Smuts and associates[308]). It would seem that methionine, the precursor of cystine, is

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304. Schoenheimer, R., Ratner, S., Rittenberg, D., and Heidelberger, M.: J. Biol. Chem. **144:** 541, 1942.

305. Whipple, G. H.: Am. J. M. Sc. **203:** 477, 1942.

306. Elman, R. and Heifetz, C. J.: J. Exper. Med. **73:** 417, 1941.

307. Holt, L. E., Jr., Albanese, A. A., Shettles, L. B., Kadji, C. and Wangerin, D. M.: Federation Proc. **1:** 116, 1942.

308. Smuts, D. B., Mitchell, H. H. and Hamilton, T. S.: J. Biol. Chem. **95:** 283, 1932.

another important amino acid in this respect. On the other hand, Lewis[309] envisages the possibility that under certain pathologic conditions it may be more desirable to eliminate one or more amino acids from the patient's diet for therapeutic purposes.

There are several avenues of approach to the treatment of protein depletion. The protein may be administered orally, in the form of either nitrogenous foods or protein digests. In some situations, however, as in pemphigus involving the mouth, where the patient is often unable to eat or even to swallow appreciable amounts of liquid foods, it is preferable to administer the protein by the parenteral route, in the form of protein hydrolysate. Moreover, in acute plasma protein deficiencies—in extensive burns, for example—parenteral infusions of protein hydrolysates may be used to supplement oral therapy in order to replenish the plasma proteins as speedily as possible. In this connection it should be noted that chronic protein deficiency is characterizd by a relatively greater loss of tissue protein than of plasma protein, while acute protein deficiencies lead to greater losses of the circulating protein.

The natural and simplest way to correct protein depletion is, of course, to give a high protein diet. One hundred and fifty Gm. of protein daily is the average amount an adult can eat, although the human organism is capable of absorbing and metabolizing larger quantities. Since a normal adult requires about 1 Gm. of protein per Kg. of body weight daily for maintenance, there remains a surplus of protein which may be used to restore tissue and blood proteins. However, only proteins of high biologic value should be given, that is, those which contain all or most of the essential amino acids. Outstanding among the foods supplying this kind of protein are: eggs, milk and dairy products, meat (if it is composed largely of muscle tissue, since cuts containing quantities of collagen and elastin have less protein value), fish, liver, kidney, soy beans, wheat, wheat germ, and brewers' yeast (in powder, flake, or chip form). The protein content of various foods is listed in Tables 98–106, pp. 574–85.

A diet intended to correct protein depletion should contain large amounts of animal protein, because all vegetable proteins are lacking in one or another of the essential amino acids. Thus, the proteins of wheat, oats, and rice are deficient in lysine, while corn meal protein is low in both lysine and tryptophan, and soy beans are low in cystine and methionine. However, when the essential acids missing from a given vegetable food are supplemented from other vegetable sources, vegetable proteins may provide a very valuable high protein intake. Thus, the abundance of methionine in corn gluten suggests the mixture of corn with soy beans to supply most of the essential amino acids. Nevertheless, since vegetable proteins are generally deficient in lysine and animal proteins are as a rule richer in this amino acid, it follows that animal proteins are more suitable for supplementing vegetable proteins than are other vegetable proteins. Table 37 lists the best sources of protein, and Table 38 gives a sample menu for the high protein diet.

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[309] Lewis, H. P.: Handbook of Nutrition. Chicago: American Medical Association, 1943.

When protein depletion has gone so far that a high protein diet alone will not suffice to correct the deficit in a reasonably short time, protein hydrolysates are indicated because they supply nitrogen in a form that is readily absorbed and assimilated. Protein hydrolysates are prepared by means of enzymic digestion. Nutramigen (Mead Johnson and Co.), produced by enzymic hydrolysis of casein, was the first preparation of this kind. Elman[310] and others have reported good results with this casein digest, both orally and intravenously. However, the value of casein is somewhat limited because it is poor in sulfur amino acids, which seem to be of particular importance for the proteins in the epidermal structures. Another valuable preparation is Aminoids (Arlington Chemical Company), which is prepared from the proteins of beef, milk, wheat, and yeast, and with which the present writer has had excellent results as a dietary protein supplement. One tablespoonful contains nitrogen equivalent to 4 Gm. of protein. The usual dosage is 1 tablespoonful four times a day, the equivalent of 16 Gm. of protein. If necessary, the daily dose may be increased to 2 or 3 tablespoonfuls of Aminoids four times a day.

TABLE 37.—*High Protein Diet*

Purpose of the diet: To provide the organism with an abundance and a variety of proteins sufficient to restore and maintain a normal nitrogen balance.

The best sources of protein are:

Lean meats
Entrails, including liver, heart, kidney, sweetbreads, tongue, tripe, lung
Poultry
Fish
Fish roe
Eggs
Skim milk
Cheese
Dried legumes (peas, beans, and lentils)
Soy beans
Whole grain cereals and breads
Gluten flour
Brewers' yeast
Nuts, including almonds, black walnuts, butternuts, pistachio
Gelatin

A high protein diet should also contain carbohydrates and fats in moderate amounts.

When oral alimentation is not feasible, or when large amounts of protein are indicated, particularly in severe cases of hypoproteinemia resulting from severe and extensive burns, the parenteral administration of protein hydrolysates, either intravenously or subcutaneously, is very helpful. Five per cent solutions of Aminoids or of Amigen in 5 per cent or 10 per cent dextrose solution are commonly employed. Parenamine (Frederick Stearns and Company) has also been found very valuable. At least 10 Gm. of amino acids can be given in one hour without spilling over into the urine. As much as 300 Gm. of protein per day can safely be administered in this manner.

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[310] ELMAN, R.: Med. Clin. North America 27: 303, 1943.

Table 38.—*Sample Menu for the High Protein Diet*

Breakfast	
Fruit	orange juice
Cereal	whole grain cereal with skim milk and sugar
Eggs	2 boiled eggs
Bread	pumpernickel, 2 slices, with liberal amount of cottage cheese
Beverage	skim milk
Luncheon	
Meat or fish	broiled steak
Vegetables	asparagus, carrots
Bread	graham bread, 2 slices, with cottage cheese
Beverage	skim milk
Dessert	fruit-flavored gelatin
Dinner	
Soup	split pea soup
Meat or fish	kidney stew
Vegetables	beans, lentils, or peas; lettuce and tomato salad
Bread	rye bread, 2 slices
Dessert	cheese and crackers

Between meals and at bedtime: 250 cc. (8 oz.) of milk with a protein hydrolysate added (Amigen, Aminoids, Parenamine).

L. HIGH SILICA DIET

Luithlen[9] was the first to call attention to the significance of silica (SiO_2) in senile pruritus, and to demonstrate that this condition responds favorably to an infusion of the herb horsetail (*equisetum arvense*), given by mouth. It is to be noted, however, that in advanced age the organism cannot absorb silica from the food with the same facility as in youth. Luithlen therefore prefers the intravenous route and gives injections of sodium silicate (1 to 2 cc. of a 1 per cent solution) daily, for a period of ten to twenty days. The present writer has employed this method for years in senile pruritus and has frequently observed very satisfactory results. The physiologic processes involved are as yet unknown. The minute quantities of silica which the organism is given in this manner can hardly be regarded as supplementation therapy.

Gorup-Besanez[311] was able to demonstrate that the silica content of feathers is directly dependent upon the nature of the bird's diet. The higher the mineral dust content of the food, the greater the silica content of the feathers. Needless to say, these observations on birds do not necessarily warrant any conclusions as to conditions in man.

An excessive intake of silica exerts a definite influence on the skin. Schulz[312] reported that following the experimental ingestion of large quantities of silica there appear in man acne pustules, furuncles, and papular exanthems, as well as an increased secretion of sour-smelling sweat and a tendency for the hair to fall out. However, no further investigation of this has been made.

Little is known about the silica metabolism in the skin, except that Schulz[312] has shown that the silica content of the skin decreases with age. This finding has been confirmed by Brown,[83] who found that 100 Gm. of fresh skin contain 7.5 mg. of SiO_2 at birth but only 2.5 mg. in an individual of very advanced age. MacCardle and co-workers[93] have demonstrated that in old age the silicon content of the nucleoli of the epidermal cells is decreased in amount.

In what form silica exists in the tissues is not known. The tissue ash is always found to contain silicon dioxide (SiO^2), and it is very likely that silicon is present in that form in the living organism (Rothman and Schaaf[41]).

M. ALTERATION (UMSTIMMUNG) DIET

As has been shown in various sections of this chapter, dietary therapy (by means of acidifying, alkalinizing, dehydrating, low sodium chloride, or raw food diets) exerts a profound influence on the organism and on inflammatory processes in the skin. Although it is unquestionably true that these various forms of diets distinctly influence the chemistry, including the physical chemistry, of the organism and notably of the skin, the writer feels, in agreement with Marchionini, Stuehmer, and other authors, that the beneficial effects of these diets are attributable in no small part to the fact that they bring about an abrupt change in the general metabolism, which, in turn, creates an otherwise unobtainable *ictus therapeuticus*. In other words, it is the sudden alteration of the dietary regimen, consisting of the gross preponderance of certain ions over others or involving extensive transmineralization, which serves to change the general state

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311. Gorup-Besanez, E. F.: Lehrbruch der physiologische Chemie. Brunswick, 1878.
312. Schulz, H.: Deutsche med. Wchnschr. **29:** 673, 1903.

of the organism and thus stimulates the underlying healing processes. Similar changes can be achieved by foreign protein therapy, fever therapy, counterirritation of the skin, and artificial infections (malaria). The Germans coined the term *umstimmung*, for which there is no precise equivalent in English, to designate this nonspecific but highly effective stimulus. This therapeutic procedure was known as metasyncrisis in antiquity (Thessalus of Tralles) and as alteration in the Middle Ages (Sylvius). It was believed that many diseases were due to the presence of abnormally alkaline or acid humors, and physicians attempted to free the organism of them by prescribing the opposite substances (*alterantia*). In other words, alteration was supposed to mean that the body, treated in this manner, became altered in that it was rid of morbid humors. Divested of its old humoral concept of pathology and considered from the modern cellular viewpoint, the principle of alteration is valid as shown in the preceding sections of this book. Therefore, the terms "alteration therapy" and "alteration diet" clearly express the alterative power of diets of this kind.

One of the most valuable forms of alteration diet is the *zigzag* diet of von Noorden,[172] with which the writer has often obtained gratifying results. The efficacy of this form of contrast diet, which we prescribe for one or two weeks as indicated, is attributable to the constant switching from foods of one type to those of an entirely different character. This is accomplished by sudden and frequent shifts from one to another of the basic constituents (proteins, carbohydrates, fat, minerals) as well as by variations in the manner of preparation of the food. Such abrupt changes produce influences of an entirely different nature on the organs of digestion, intermediary metabolism, and excretion. In short, this dietary method is effective because it definitely leads to "alteration."

TABLE 39.—*Modified Zigzag Diet*

Day	Type of Diet
1, 2	Raw food diet, consisting exclusively of raw fruits and raw vegetables and their juices
3, 4	High protein diet (meat, fowl, fish, legumes, cottage cheese)
5, 6	High carbohydrate diet (breadstuffs, potatoes, rice, honey, syrup, jam, marmalade, sugar, tea, bananas, grapes, raisins)
7	Normal diet
8, 9	Acidifying diet (see Table 11) plus ammonium chloride, 1 Gm. four times daily
10, 11	Low salt diet (raw and cooked fruits and vegetables, milk, cream, salt-free bread, eggs, sugar, tea, marmalade)
12, 13	High fat diet (fat meats, butter, turkey, duck, salmon, tuna fish, cream, breadstuffs, pastries, margarine)
14	Normal diet

An especially effective, but very drastic, alteration diet is the thirst and hunger diet introduced by Schroth.[313] The present writer has found this regimen to be helpful, notably in the treatment of severe, unmanageable, and therapy-resistant cases of dermatitis, urticaria, and elephantiasis.

TABLE 40.—*Schroth's Treatment*

This regimen consists of a hunger and thirst diet, purgation, and hydrotherapy. Its purpose is:

1. Radical increase in excretion of the waste products of metabolism by all avenues, particularly through the skin.
2. To produce extreme alteration in the body by means of a dietary free of animal protein and fats of all kinds and low in calories, salt, and roughage.
3. To alter the water balance between blood and tissues by regularly changing from so-called dry to wet days every forty-eight hours.

TABLE 41.—*Sample Weekly Schedule for Schroth's Treatment*

Begin gradually as follows:

First day:	Bowel evacuation with a saline purge or enema
	Until noon: only toasted bread, as much as desired
	Noon: 250 to 500 Gm. (8 to 16 oz.) oatmeal or rice porridge with plums
	4 p.m. until supper: 125 to 100 cc. of warm white wine with toast (or in place of wine, the other liquids mentioned below)
	7 p.m.: gruel made from rice, farina, or potatoes
	Bedtime: cold packs to secure hyperemia
Second day:	Until noon: only toast or zwieback
	Noon: 250 to 350 Gm. of porridge with applesauce
	4 p.m. until bedtime: 500 cc. of tea, fruit juices, or wine
	Evening: cold packs
Third day:	No liquids, only toast
	Evening: 125 cc. (4 oz.) of liquids; cold packs

After the first three days continue as follows:

Mondays and Thursdays: the same as for the first day
Wednesdays and Saturdays: the same as for the second day
Tuesdays, Fridays, and Sundays: the same as for the third day

The average length of this regimen is three weeks.

Additional recommendations: Liquids to be taken only at the prescribed times. Washing and mouth cleansing only with tepid, not cold, water. In applying the cold packs at night, ice-cold water should be used in order to promote active hyperemia of the skin, which follows when the compresses are removed. Black coffee should be given if the heart action is very slow (typical of first week) or if the patient feels weak. To combat insomnia which often occurs in the first week, give tincture of Valerian 4 cc. (1 dram).

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[313] SCHROTH, K.: Personal communication.

Outline of Schroth's Treatment

Diet: The patient may eat at his discretion 100 to 150 Gm. (3 to 5 oz.) of toast, stale rolls, or old salt-free bread every day in the week.

On two days a week, the patient should take at noon between 250 to 500 Gm. (8 to 16 oz.) of fat-free, salt-free porridge or gruel made of oatmeal, millet, barley, rice, potatoes, or tapioca, boiled in water. This should be flavored with lemon juice, prune juice, dried prunes, or applesauce. If necessary, to combat weakness, such porridge may be given again in the evening. On two other days the porridge or gruel is served only once a day and only 250 Gm. (8 oz.) in addition to unlimited amounts of stale bread. On three days of the week only toast or stale rolls may be eaten.

Liquids: On the four days on which the porridge is given, the patient should *sip* 500 to 1,250 cc. (16 to 40 oz.) of very light wine, starting at 3 p.m., along with some toast. Nonalcoholic fruit juice or warm, weak, unsweetened tea can be substituted for the wine. A cup of black coffee may be taken occasionally.

On the three "dry days" no liquids are to be taken, with the possible exception of 125 cc. (4 oz.) of wine or tea at night. The patient may suck a few lemon slices if he is very thirsty.

Three times weekly the bowels should be evacuated by means of a saline purge or an enema.

Whenever possible, for three or four hours at night apply cold packs to the entire body to secure a diffuse hyperemia of the skin.

N. ALCOHOL-FREE DIETS

There are several ways in which ethyl alcohol may influence diseases of the skin: (1) by its effect on the nervous system; (2) by its effect on the circulation; and (3) by its effect on metabolism. Each of these actions is likely to have a profound influence on the production and duration of cutaneous affections.

By its sedative influence on the medulla, alcohol causes vasodilatation by reducing vasoconstriction of the capillaries of the skin, and the sense of flushing, after imbibing alcohol in any quantity, is the commonly recognized result. The dilatation of the cutaneous capillaries leads to a greater flow of blood to the surface of the body and, of course, to greater congestion in affected areas; and this congestion is most difficult to control in many of the dermatoses. Through its vasodilator action, alcohol markedly increases the secretion of sebum, causing the skin to become greasy. According to Montgomery,[257] alcohol may very well cause or intensify seborrhea in still another manner. Since alcohol is more readily oxidized than either fat or starch or sugar, it spares these from oxidation. The ingested fat is, therefore, not burned but shunted into fat repositories, and the starch and sugar are converted into fat and are similarly shunted and stored. This increase of fat would tend to intensify seborrhea (see p. 403).

Alcoholic beverages may occasionally cause and frequently do aggravate allergic manifestations such as dermatitis, urticaria, and seborrhea, by increasing the permeability of the gastrointestinal tract, thus facilitating the absorption of insufficiently digested food proteins into the blood stream.

On the basis of these considerations it is important to exclude alcohol in all forms from the diet in certain dermatoses, particularly seborrhea and rosacea.

PART TWO

NUTRITIONAL CAUSES OF DERMATOSES

In the following pages we shall present a discussion and critical review of those cutaneous manifestations and skin diseases which are primarily or principally due to nutritional causes. The great progress that has been made in the study of the vitamins and of the biochemistry of the three basic constituents of our food (proteins, carbohydrates, and fats) now enables us to classify as belonging to the nutritive group a number of cutaneous manifestations whose etiology and pathogenesis have hitherto been doubtful or obscure. Moreover, we now have a far better understanding of dermatoses due to food hypersensitiveness, thanks to the extensive work that has been done in the field of allergy. Skin diseases caused by alimentary infections and intoxications will also be discussed in this section.

CHAPTER III

Skin Diseases Due to Malnutrition

Pathologic states due to nutritional causes, in man and in animals, are the results of adherence to a diet that is improper, either in quantity or in composition. Thus, nutritional damage may be divided into quantitative and qualitative categories, and both groups may be subdivided into diseases of overnourishment and undernourishment.

A. QUANTITATIVE CAUSES OF MALNUTRITION

1. General Overnourishment

Overnourishment commonly leads to what is known as dietary or exogenous obesity. This condition not infrequently predisposes to intertriginous dermatoses, caused principally by friction between skin surfaces and by the maceration of the skin resulting from accumulated moisture in the skin folds. Such maceration in turn often leads to staphylococcic infections or to fungous diseases (dermatophytosis, moniliasis). Furthermore, this form of obesity frequently activates a latent diabetic tendency, whereupon any of the numerous dermatoses described in Chapter II, notably furunculosis, may make its appearance. In all cases of this kind, weight reduction by means of an appropriate diet, together with local dermatologic treatment, will generally be successful.

The danger of overnourishment in infants lies in two directions: in some children it results in excessive fattening, and in a smaller percentage of cases it leads to acute intestinal disturbances (diarrhea). Furthermore, it tends to have a harmful effect on the entire organism in that it lowers the body's general resistance. Overnourishment exerts a particularly harmful effect on children with an exudative diathesis. Here it does not merely lead to an excessive accumulation of depot fat, as in constitutionally normal children, but it produces instead flabby, fatty tissue with a high water content and predisposes the skin to dermatitis. In the section on infantile dermatitis we shall discuss this question in greater detail and show that in exudative children reasonable dietary restrictions not infrequently lead to gratifying results that cannot be achieved by any form of medication.

2. General Undernourishment

In the state of inanition which not uncommonly results from severe gastric and intestinal diseases, the skin assumes a pale, sallow color, becomes dry and inelastic, presents an unusual pigmentation (chloasma cachecticorum), scaling, a tendency to bleed (purpura cachecticorum), and manifests distinctly impaired powers of resistance to all manner of irritations and infections. J. Jadassohn[220] includes some cases of what is known as acne cachecticorum in this category. Rous[314] observed that the rate of growth of tumors was relatively slower in undernourished animals, and the same observation was made in man during the first World War. Moreover, inadequate nutrition, particularly in proteins leads to so-called nutritional edema, which is discussed in the section on protein deficiency (p. 139).

The present author[315] described nail dystrophies following long periods of undernourishment. J. Jadassohn[220] regards Lanz's observation on himself of the formation of transverse striae on the finger nails after a few months' adherence to a vegetarian diet as a demonstration of the effect of the diet on the skin and its appendages.

B. QUALITATIVE CAUSES OF MALNUTRITION

1. Specific Overnourishment

a. Overnourishment with Lipochrome (Carotenoids)

"Lipochrome" refers to a colored substance associated with fat. The early recognition of carotene, and its importance among the lipochromes, has led to the use of the term "carotenoids" to denote this class of substances. The term "carotenemia" was introduced by Hess and Myers[316] to cover the entire clinical picture of yellow skin and abnormally high carotene levels in the blood, and Gandy[317] proposed "carotenoderma" to designate the cutaneous manifestations. It must be borne in mind, however, that the yellow color of the skin is not always due to carotene alone.

Baelz,[318] in the year 1896, was the first to describe a yellowish pigmentation of the skin and to term it "aurantiasis." In 1904 von Noorden[319] called attention to the fact that diabetics not uncommonly present such yellowish pigmentation, which he chose to call "xanthosis." Numerous cases have since been reported, notably during the past decade, and it is believed that they may be attributed to the fact that the consumption of vegetables and eggs has greatly increased in recent years. An adequate understanding of this syndrome is required to enable the physician to differentiate between this condition and an obscure, long-standing case

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314. Rous, P.: J. Exper. Med. **20:** 433, 1914.
315. Urbach, E.: Zentralbl. f. Haut- u. Geschlechtskr. **11:** 290, 1924.
316. Hess, A. F. and Myers, V. C.: J. A. M. A. **73:** 1743, 1919.
317. Gandy, D. T.: South. M. J. **28:** 444, 1935.
318. Baelz: Cited after Miyake, I.: Arch. f. Dermat. u. Syph. **147:** 184, 1924.
319. von Noorden, C. H. and Salomon, H.: Handbuch der Pathologie des Stoffwechsels, 1907.

of mild jaundice. Moreover, patients with extensive carotenoderma are easily fatigued, may have paresthesias of the extremities, and in some exceptional cases, may even present enlargement of the liver and spleen (Henschen,[320] Josephs[321]). Clinically, this yellowish pigmentation of the skin is distinguished from icterus by its distribution (nasolabial folds, palms, and soles); by the normal bilirubin level in the blood serum; by the color of the urine, which is normal and not dark; and, chemically, by an increase in the lipochrome pigment in the blood (see Table 42). Synonyms for this condition are: carotenoderma, caretenosis cutis, aurantiasis, xanthosis cutis, and hyperlipochromoderma.

Carotene is the yellow coloring matter found in carrots, spinach, pumpkins, sweet potatoes, kale, parsnip, papaya, yellow squash, yellow turnips, green or yellow beans, oranges, and palm oil. Four distinct forms of carotene are known—alpha-carotene, beta-carotene, gamma-carotene and cryptoxanthin—all of which are precursors of vitamin A. The isomer of carotene, lycopene, the coloring matter of tomatoes, watermelons, and bittersweet berries, is physiologically inactive in that it plays no role in so far as the formation of vitamin A is concerned. Certain carotenoid pigments contain oxygen and are known as xanthophylls. The xanthophyll of alpha-carotene is lutein, which gives the color to egg yolk. Further more, many green plants contain xanthophyll, whose yellow hue is usually masked by the intense green of chlorophyll.

The absorption of lipochromes in the intestines depends on the presence of adequate quantities of dietary fat and of bile. Curtis and Ballmer[323] have shown that liquid paraffin impedes the transfer of carotene through the epithelium of the intestine. The conversion of carotene into vitamin A probably takes place in the liver.

According to Wood and Agnor[324] any excess of carotene is either destroyed in the body or excreted in the sweat. Histologic examination discloses that carotene resides principally in the superficial horny layer of the skin and that its concentration becomes lower in the deeper strata. This is generally explained by the assumption that when excretion through the pores is unusually heavy, some of the lipochrome is reabsorbed by the horny layer of the skin. This theory would seem to gain strong support from the fact that carotene is found predominantly in those areas in which the horny layer is particularly thick (palms, soles), or in which sebaceous glands abound (forehead, nasolabial folds), or where sweating is most marked (axilla, groin).

[320] Henschen, C.: Schweiz. med. Wchnschr. **71:** 331, 1941.
[321] Josephs, H. W.: Am. J. Dis. Children **67:** 33, 1944.
[322] Jeghers, H.: New England J. Med. **228:** 678 and 714, 1943.
[323] Curtis, A. C. and Ballmer, R. S.: J. A. M. A. **113:** 1785, 1939.
[324] Wood, R. H. and Agnor, E. B.: J. M. A. Georgia **30:** 239, 1941.

In most cases carotenoderma is quite simply the result of a diet excessively rich in foods containing carotenoids. That there are variations in the tendency of individuals to develop this pigmentation is evidenced most strikingly by the fact that the great majority of vegetarians remain unaffected. Children seem more prone to develop carotenoderma than do adults. It is particularly interesting to note the observation that an infant may exhibit yellowish pigmentation of the skin after as brief a period as two months on the breast milk of its carotenemic mother (Almond and Logan,[325] Pariente and associates[326]). According to Hess and Myers[316] and Dollinger,[327] a certain amount of exposure to sunlight is required to induce carotenoderma. This view is supported by: (1) the fact that the condition involves almost exclusively those skin areas that are exposed to light, notably the face; (2) the fact that it invariably makes its appearance in the summer; (3) the experimental findings of Klose[328] that, of a group of infants given exactly the same food, the yellow pigmentation could be produced only in those whose cribs were kept near a window.

It is also possible to produce pigmentation of the skin in experimental animals. Thus Ansai[329] saw white mice turn yellow when kept on a diet of bread containing raw carotene derived from pumpkins. Other authors have reported similar observations in monkeys following a diet limited to carrots.

Almond and Logan[325] find that the threshold quantity appears to be a minimum of 4 pounds of carrots per week for a minimum period of seven months in addition to the individual's usual consumption of carrots, before skin pigmentation becomes visible. Fading is first noticed two weeks after carrots have been eliminated from the diet and is usually complete within eight weeks. However, the pigmentation may persist for many months after they have been stopped. These authors believe that, when the threshold quantity is exceeded, the body is unable to oxidize or excrete all the lipochrome, with the result that there is a slow and constant accumulation of pigment. They explain the relatively frequent occurrence of carotenoderma in diabetics by the fact that the latter are so often kept on a diet containing an abundance of fruits and vegetables which are rich in lipochrome and by the assumption that the ability of the liver to convert carotene into vitamin A is impaired in diabetics.

Duncan[203] is of the opinion that the xanthosis occurring in diabetes is a result of a disturbance of the carbohydrate metabolism. He found that,

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325. Almond, S. and Logan, R. F. L.: Brit. Med. J. 2: 239, 1942.
326. Pariente, A. C., Present, C. H., and Ralli, E. P.: Am. J. M. Sc. **192**: 365, 1936.
327. Dollinger, A.: Med. Klin. 17: 1553, 1921.
328. Klose, E.: Münch. med. Wchnschr. 66: 419, 1919.
329. Ansai, M.: Trans. Jap. Path. Soc. 16: 133, 1926.

compared with normal subjects, diabetic children were very slow in reducing an artificially increased carotene content of the blood to normal levels. Heyman,[330] in a series of carotene tolerance tests on normal and diabetic children, observed that the latter are incapable of utilizing carotene properly. The somewhat higher incidence of carotenoderma in nephritis is attributed to inadequate urinary excretion of the pigment. Josephs,[321] on the other hand, stresses the correlation of high carotene and high lipid levels in the blood and explains the frequent occurrence of carotenemia in patients with diabetes, nephrosis, and hypothyroidism on the basis of the associated hyperlipemia.

Since carotenoderma is so commonly observed in diabetics, the presence of this skin condition should always suggest the possibility of an underlying diabetes mellitus.

Patients often have a mild degree of carotenemia without any noticeable carotenoderma. The blood carotene threshold necessary to produce visible skin manifestations probably is different in various individuals. According to Stueck et al.[331] the average normal serum value is 0.11 mg. These authors estimate that carotenoderma makes it appearance when the serum carotene level reaches from two to five times the normal values.

The presence of the pigment may be demonstrated spectrographically or chemically but most simply by shaking the blood serum with petroleum ether.

Greene and Blackford's[332] three layer test makes possible the diagnosis of carotenemia despite the presence of excess quantities of bilirubin in the blood. Equal portions of serum, alcohol, and petroleum ether, shaken together in a tube, separate into three layers on standing. The top layer, of petroleum ether, contains the lipochrome pigments, the middle layer (alcohol) holds the bilirubin, and the serum proteins are precipitated in the bottom layer.

Table 42 (p. 136) presents the pertinent differences between carotenoderma and jaundice, as summarized by Jeghers.[322] However, Elmer and Scheps[333] have confirmed observations reported by Umber and Miyake that some patients with carotenoderma present yellow coloration of the conjunctivas and other mucosa. One must be cautious, therefore, in using this symptom to differentiate between xanthosis and icterus. A paper by Wise and Diasio[334] contains four excellent colored plates illustrating the appearance of the face, palms, soles, and blood serum of a patient with carotenoderma.

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330. Heyman, W.: J. A. M. A. **106:** 2050, 1936.
331. Stueck, G. H., Flaum, G., and Ralli, E. P.: J. A. M. A. **109:** 343, 1937.
332. Greene, C. H. and Blackford, L. M.: M. Clin. North America **10:** 733, 1926.
333. Elmer, A. W. and Scheps, M.: Klin. Wchnschr. **8:** 300, 1929.
334. Wise, F. and Diasio, F. A.: Arch. Dermat. & Syph. **20:** 862, 1929.

TABLE 42.—*Differential Features of Carotenemia and Jaundice (Jeghers[322])*

Differential Features	Carotenemia	Jaundice
Pigment responsible for the yellow color	Carotenoid (lipochrome) pigments	Bilirubin
Areas where pigmentation is first noticed	Forehead, nasolabial folds, palms, soles, and over pressure areas	Sclera, mucous membrane under tongue, and body areas with thin skin
Extent of pigmentation when of severe degree	Entire skin, with accentuation in areas mentioned above	Entire skin, sclera, and mucous membranes; least on palms and soles
Sclera	Free of pigment	Pigmented
Mucous membranes	Usually free of pigment	Pigmented
Color of pigment	Canary or lemon yellow	Yellow with green, bronze, orange, or saffron tint
Urine	No significant color change	Except for "retention" jaundice, dark from presence of bilirubin
Stool	No change	Clay-colored in obstructive jaundice; normal or darker in other types of jaundice
Icteric index (potassium dichromate standards)	Increased	Increased
Blood bilirubin (quantitative van den Bergh test)	Normal	Increased
Greene and Blackford's three-layer test	Lipochrome yellow pigments in top petroleum ether fraction	Yellow bilirubin pigment in center alcohol layer
Dietary history	Excess ingestion of foods rich in carotenoid pigments	Generally not significant as an etiologic background
Diseases accentuating or responsible for its production	Diabetes mellitus, kidney failure, myxedema, liver disease, and possibly other endocrine disorders	Except for liver disease, other diseases responsible for carotenemia do not as a rule cause jaundice
Itching of skin	Not present	Frequent
Effect on health	No effect on health	Almost always a serious condition

TABLE 42.—*Continued*

Differential Features	Carotenemia	Jaundice
Duration	Lasts as long as foods rich in lipochromes are consumed in excessive amounts (weeks to months or more)	Varies with type of jaundice
Time required to produce disease	Several months of excess ingestion of foods rich in lipochrome pigments	Days to weeks
Transmitted by breast milk to nursing child	Yes	No

While the treatment of carotenoderma consists in temporarily restricting the consumption of foods rich in lipochromes, chiefly carrots, spinach, sweet potatoes, pumpkins, squash, corn, butter, and egg yolk, care should be taken not to interfere with the intake of vitamins and minerals. Yeast concentrate and vitamins A and D should be administered. Skim milk will provide the necessary calcium. Ferric ammonium citrate, 2 to 4 Gm. (30 to 60 grains) daily, should be given during the period of rigid restriction.

b. *Overnourishment with Table Salt*

Schulz[335] describes skin manifestations resulting from a dietary excessively high in table salt content or following the use of mineral water rich in sodium chloride. These include tenderness of the scalp and increased secretion of the sebaceous glands, a tendency to loss of hair, and weeping dermatitis. Occasionally the entire skin takes on a peculiar dirty appearance and becomes shriveled. According to Schulz[335] a further characteristic reaction to an excess of table salt is disproportionately profuse sweating which follows any bodily exertion.

c. *Overnourishment with Vitamins (Hypervitaminosis)*

Some of the carotenoids are precursors of vitamin A (provitamin A) (p. 152), but others are not related to vitamin A activity. For this reason overnourishment with carotenoids was dealt with in a separate section.

Despite widespread use of vitamin A for many years, very few reports of toxic symptoms of hypervitaminosis A have appeared. However, according to Schwemmler[336] large doses may cause injury to the nails, which become thin, brittle, lose their homogeneous structure, and acquire conspicuous transverse indentations. In addition, there may be loss of hair, weakness, and emaciation.

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[335] SCHULZ, H.: Vorlesungen über Wirkung und Anwendung der unorganischen Arzneistoffe. Leipzig: Thieme, 1920.

[336] SCHWEMMLER, B.: Münch. med. Wchnschr. **86:** 1226, 1939.

Sutton and Sutton[337] reported epidemics of acne caused by the wholesale administration of cod liver oil and its concentrates in institutions caring for children. They believe that this is due to the antagonism between the vitamin A content of the oil and thyroid secretion. High doses of vitamin A may cause anorexia, nausea, emaciation, and even enlargement of the liver and spleen. In experimental animals, excessive amounts have produced reactions, in some cases so severe as to cause death. However, no toxicity has been reported with dosages lying within the therapeutic range even for serious deficiency states.

Vitamin C does not produce cutaneous manifestations in adults when given in ordinary therapeutic doses (up to 500 mg. daily). A marked and prolonged vasodilatation of the cutaneous vessels was observed in infants following extremely large doses (650 to 850 mg.) by Wiedenbauer.[338] The skin manifestations consisted of increased dermographism, hyperemia, morbilliform or scarlatiniform eruptions, often even urticaria and edema, and were accompanied by intestinal hyperperistalsis.

After excessively large quantities of vitamin D Pfister[339] noted the appearance of acute facial dermatitis, which subsided when vitamin therapy was discontinued. Feer,[340] Jadassohn and Schaaf,[341] and Rodecourt[342] described generalized pigmentation which occurred in children with dark skin and hair but not in children with fair complexion. It is believed that the pigmentary effect is due to relative deficiency of vitamin C caused by disturbance in the physiologic relationship between the vitamins when one of them is given in excessive quantities.

2. Specific Undernourishment

Before discussing the nutritional deficiency diseases, it will be instructive to cite Kruse's[343] and Jolliffe's[344] concept of malnutrition. According to these authors malnutrition may be brought about (1) by a primary deficiency arising from an inadequate intake of essential nutrients (primary malnutrition) or (2) by a secondary deficiency produced by conditioning factors (secondary malnutrition). The latter may occur even in the presence of dietary adequacy. The conditioning factors include those

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337. Sutton, R. L. and Sutton, R. L., Jr.: Diseases of the Skin. St. Louis: Mosby, 10th ed., 1939.
338. Widenbauer, F.: Klin. Wchnschr. **15:** 815, 1936.
339. Pfister, F. F.: J. A. M. A. **102:** 533, 1934.
340. Feer, E.: Schweiz. med. Wchnschr. **8:** 1275, 1927.
341. Jadassohn, W. and Schaaf, F.: Ztschr. f. Vitaminforsch. **4:** 324, 1935.
342. Rodecourt, M.: Münch. med. Wchnschr. **76:** 1420, 1929.
343. Kruse, H. D.: Milbank Mem. Fund Quart. **20:** 245, 1942.
344. Jolliffe, N. and Smith, J. J.: M. Clin. North America **27:** 567, 1943.

which interfere with the ingestion, absorption, or utilization of essential nutrients or which increase their requirement, destruction, or excretion. In other words, we must distinguish between dietary and nutritional inadequacy in diseases due to malnutrition.

In the discussion which follows the importance of conditional malnutrition is so great that we present in Table 43 the excellent summary of Jolliffe and Smith.[344]

a. Protein Deficiency

In the vast majority of cases of protein deficiency the chief manifestation is nutitrional edema. Synonymous terms are "hunger edema," "war edema," "prison edema," and "alimentary dropsy." These connotations graphically designate the circumstances and situations which most commonly lead to the condition. Countless instances of this disease have been observed during periods of famine, notably in India and in China, and also in times of war, as in Germany and Austria during World War I and in the occupied countries during the second world-wide conflict. Nutritional edema was very common in European and American prisons as recently as the nineteenth century. Moreover, endemic nutritional edema has been reported in certain areas of the South in the United States (Youmans[132]). In the wards of larger hospitals are seen sporadic cases attributable to a wide variety of causes, ranging from food faddism to severe organic disease, particularly of the gastro-intestinal tract, interfering with digestion and absorption. Finally, nutritional edema may be encountered in children fed a preponderantly carbohydrate dietary.

The primary etiologic factor in nutritional edema is a continuously inadequate nitrogen intake, possibly aggravated by a diet insufficient in calories. This disorder is associated with hypoproteinemia. The decreased concentration of the serum proteins lowers the colloid osmotic pressure of the blood and permits the passage of increased amounts of fluid from the blood into the tissues, thereby causing edema. The hypoproteinemia is almost always the result of hypoalbuminemia. Bruckman and Peters[345] found the critical range for the development of edema to be 3 to 4 Gm. of albumin per 100 cc. of blood.

Clinically, the essential feature of this disease is an edema which varies in extent and intensity from slight pitting of the legs on pressure to ascites and even anasarca. Occasionally the skin is red and hot, as though infected. Posture, by affecting capillary pressure through variations in hydrostatic pressure, is responsible for the common observation that in bed-fast patients the legs are swollen in the evening, the face and hands in the morning. The onset is gradual as a rule, but the manifestations

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[345] Bruckman, F. S. and Peters, J. P.: J. Clin. Invest. 8: 591, 1930.

TABLE 43.—*Conditioning Factors Which May Contribute to Nutritional Failure (Jolliffe and Smith*[344]*)*

I. *By Interfering with Food Intake*
  1. Gastro-intestinal diseases, as:
    - Acute gastro-enteritis
    - Cholecystitis and cholelithiasis
    - Peptic ulcer
    - Diarrheal diseases
    - Carcinoma of stomach and esophagus
  2. Food allergy
  3. Mental disorders, as:
    - Neurasthenia
    - Neurosis
    - Psychoneurosis
    - Psychosis
  4. Operations and anesthesia
  5. Infectious diseases associated with anorexia
  6. Loss of teeth
  7. Heart failure (anorexia, nausea, and vomiting by visceral congestion)
  8. Pulmonary disease (anorexia and vomiting due to cough)
  9. Toxemia of pregnancy (nausea and vomiting)
  10. Visceral pain (as in renal colic, and angina that reflexly produces nausea and vomiting)
  11. Neurologic disorders which interfere with self-feeding
  12. Migraine

II. *By Interfering with Absorption*
  1. Diarrheal diseases, as:
    - Ulcerative and mucous colitis
    - Intestinal parasites
    - Intestinal tuberculosis
    - Sprue
  2. Gastro-intestinal fistulas
  3. Diseases of liver and gallbladder
  4. Achlorhydria
  5. Carcinoma of the stomach

III. *By Interfering with Utilization*
  1. Liver disease
  2. Diabetes mellitus
  3. Chronic alcoholism

IV. *By Increasing Requirement*
  1. Abnormal activity, as associated with prolonged strenuous physical exertion with lack of sufficient sleep or rest, delirium and manic-depressive psychoses
  2. Fever
  3. Hyperthyroidism
  4. Pregnancy and lactation

TABLE 43.—*Continued*

V. *By Increasing Excretion*
  1. Biliary or gastro-intestinal fistula
  2. Perspiration
  3. Loss of protein in nephritis and nephrosis
  4. Polyuria, as in:
    Diabetes mellitus
    Diabetes insipidus
    Long-continued excessive fluid intake, as in urinary tract infections
  5. Lactation

VI. *By Therapeutic Measures*
  1. Therapeutic diets, as in:
    Sippy regimen
    Gallbladder disease
    Anti-obesity diets
  2. Antacids
  3. Mineral oil
  4. Infusions
  5. Diuretics
  6. Fever therapy
  7. Paracentesis and thoracentesis

may make a sudden appearance following unusual exertion or after taking large amounts of water and salt (Youmans[132]). In chronic cases such change as induration of the tissues and pigmentation of the skin may occur. In addition to edema, the patients suffer from anemia, weakness, fatigue, and mental depression.

To establish the clinical diagnosis, edema due to other causes (cardiac, renal, pregnancy) must be ruled out, and subnormal blood protein levels must be present.

In the majority of cases treatment of nutritional edema is simply a matter of providing adequate food. Care must be taken, however, to supply sufficient amounts of protein of a high biologic value. Animal protein will relieve the edema and restore the serum protein level to normal more quickly than will vegetable protein.

The question of protein deficiency states in infants warrants special consideration. Younger children are particularly prone to edema because their serum protein level is lower than in adults even under normal conditions, and their need for protein is therefore relatively greater. Protein deficiency was formerly frequently seen in infants whose diet consisted largely of a porridge of flour with large quantities of salt added and possibly also some sugar. Although this mixture is rich in carbohydrates and in water-binding salts, it is lacking in protein, fat, and calcium. An inadequate diet of this kind was employed for long periods, mainly during the treatment of persistent diarrhea. The porridge succeeded in controlling the diarrhea, but fear of its recurrence if the child were restored to a normal milk diet impelled many a mother to continue with the unbalanced flour diet for weeks and even months.

Cereal grains contain approximately 60 per cent carbohydrate, small quantities of calcium and sodium, and a little organically bound sulfur. The relatively small amounts of protein are poor in leucine and cystine. Fat is also lacking.

The effects of a preponderantly flour diet on the living organism are strikingly displayed when a guinea pig is kept on a regimen limited to flour and vitamins for a long period. After approximately three weeks, during which the animal shows a rapid increase in weight, edema makes its appearance, together with pronounced gaseous abdominal distention and a partial loss of coat. At this point many of the animals succumb to infections; but the seriously ailing animals can be saved and completely cured in a few days if a normal, well balanced diet is resumed in time. The fact that animals fed on wheat rolls and sugar have a high water content was demonstrated many years ago by Voit and Weigert, who showed that while the tissues of rabbits on this diet contain an average of 85 per cent of water, the corresponding figure for animals on a cream diet is 72 per cent.

In infants, malnutrition due to flour manifests itself in two forms: (1) the hydremic form, which corresponds to the period of excessive water retention, and is generally followed by (2) the atrophic form, during which the loosely bound water is eliminated. The presence of severe dystrophy or atrophy due to extensive tissue damage, previously hidden from the inexperienced observer by an apparent gain in weight, thus becomes evident (Meyer and Nassau[346]).

Nutritional damage due to dietaries limited to flour exerts an extraordinary influence on the organism's powers of resistance. Extensive and refractory furunculosis and pyoderma may occur and often will prove fatal in an amazingly short time, since the undernourished children are utterly incapable of coping with these infections. Treatment consists chiefly in giving an appropriate diet, including adequate amounts of protein. When such food is not tolerated, the various protein hydrolysates will serve as an excellent substitute.

Figure 35 shows the pasty appearance of a child of 6 months whose diet consisted of porridge with very little milk and no vegetables or fruit juices whatsoever. The face is strikingly pale; the skin is covered with numerous furuncles (Fig. 36). When the diet was corrected the furun-

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346. Meyer, L. F. and Nassau, E.: Die Sauglingsernährung. Bergmann, 1930.

culosis cleared up within fourteen days, without any special external treatment.

Protein deficiency is not infrequently encountered in children who because of milk allergy are placed on elimination diets. The treatment of this condition is dealt with in the section on allergy (p. 243).

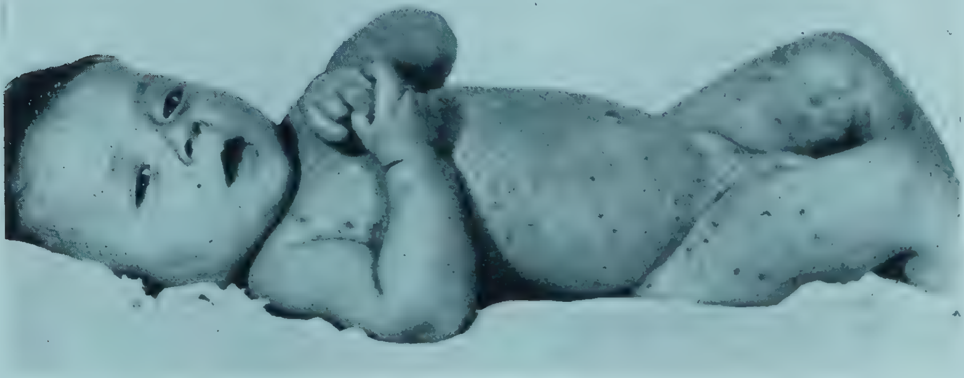

FIG. 35. PASTY APPEARANCE OF A 6 MONTH OLD CHILD DUE TO MALNUTRITION BECAUSE OF AN EXCLUSIVE FLOUR DIET
Note the striking pallor of the face

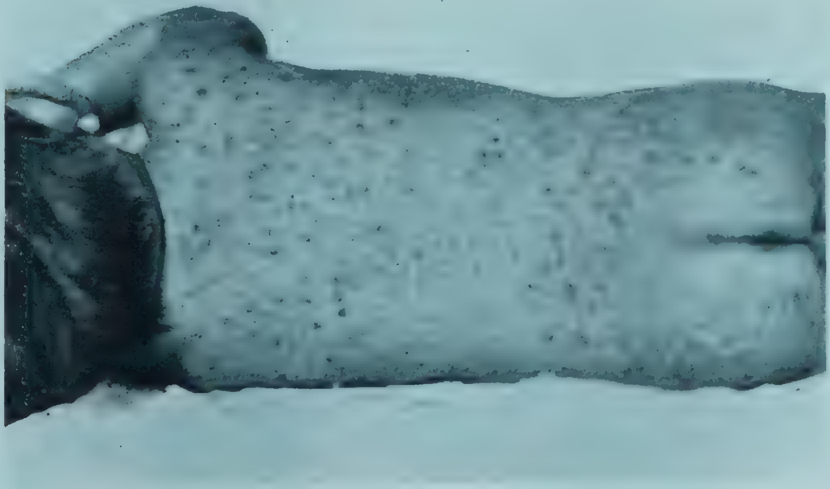

FIG. 36. FURUNCULOSIS DUE TO AN EXCLUSIVE FLOUR DIET
This is the same child as in Fig. 35

b. Carbohydrate Deficiency

Carbohydrate deficiency has been observed only in children and in experimental animals. When a child is kept for a long time on a diet consisting of large amounts of milk with little or no sugar, its development is affected in a rather typical manner. Although children on such a diet receive more than their normal caloric requirements, they fail to gain weight and a number of characteristic general manifestations make their appearance: pallor, loss of muscle tonus, lowered turgor, decreased immunity. As an indication of the functional disturbance of the gastro-intestinal tract, the feces take on a soapy appearance, that is to say, chalky white or grayish, crumbly dry stools which do not adhere to the diapers and which because of their light color seem to lack bile pigment.

Since nutritional disturbances due to a diet limited to milk are observed only in isolated instances, it must be assumed that the affected child is especially predisposed in this direction.

In human milk, which is of course the natural prototype of all artificial food mixtures and in which the nutritive components are present in proportions best suited to the growing infant's requirements, the ratio of fats to carbohydrates is approximately 1:2; however, in whole cow's milk and in unsweetened diluted milk the ratio of fats to carbohydrates is 1:1.

The fact that growth and development are closely related to the optimum ratio between the dietary constituents can also be demonstrated in growing animals for the special case of nutritional damage due to a regimen limited to milk. When young guinea pigs are kept on a diet rich in fat and protein, poor in carbohydrates, and containing enough salts and vitamins to meet the requirements of the growing organism, the animals will begin to show signs of faulty development, in many respects resembling the manifestations of nutritional damage due to a diet consisting solely of milk. They cease to gain weight, their growth is appreciably retarded, and their coats show characteristic changes.

Thus, an insufficiency of carbohydrates in the diet makes itself felt in two distinct ways: (1) the requirements of the growing cells remain unsatisfied; and (2) abnormal processes take place in the gastro-intestinal tract, notably excessive putrefaction resulting from the wealth of protein in the diet.

That carbohydrate insufficiency is the decisive factor in causing nutritional changes due to milk dietaries is demonstrated by the fact that only the addition of carbohydrate to the diet suffices to clear up the intestinal disturbances as well as all other manifestations.

c. Water Deficiency

Water deficiency as a cause of malnutrition has been observed only in very young children.

If the water intake is permitted to fall below a certain level, manifestations of disease are likely to make their appearance. The water requirements of infants vary considerably, ranging between 80 and 200 cc. per kilogram of body weight; therefore, a fluid intake of 75 cc. per kilogram must be regarded as the absolute minimum.

We recognize two different clinical pictures caused by water deficiency. First, there is the form that manifests itself acutely and abruptly, developing within a few days and sometimes even in a few hours. This condition is marked by hyperthermia, loss of weight, and general malaise. The children look pale, grayish; they have dark shadows under their eyes; their lips, as well as the oral mucosa, are red, fissured, and dry. The fontanels are depressed; the skin is flaccid, dull, and dried out.

The effects of water deficiency can also manifest themselves in a subacute or chronic form which is not distinguished by any special clinical symptoms. The damage due to malnutrition is seen principally in the fact that the child fails to gain weight despite an adequate intake of calories.

It should be noted that relatively large amounts of water are required by children who are on formulas containing large quantities of protein and salt. We stress this point most particularly because there is a school of thought which holds that fluid restriction is of especial value in the management of dermatitis on the basis of exudative diathesis in children.

d. Vitamin Deficiency

Vitamins are organic substances which in very minute quantities are necessary for the proper functioning of the organism and which, in general, must be obtained preformed from outside sources. However, newer investigations of Elvehjem have demonstrated that intestinal bacteria can synthesize certain vitamins such as thiamine and riboflavin, depending on the type of diet which the animal was fed. The synthesis apparently varies in different species of animals, but up to the present writing it is not an established fact in human beings. The only known exception is vitamin D, which, interestingly enough, is formed in the skin under the influence of sunlight.

It is highly probable that vitamins produce their physiologic effects largely through the mechanism of enzyme action, i.e., by altering the rates of chemical reactions involved in metabolism (Gordon and Sevringhaus[347]). Moreover, at least three members of the B complex, i.e., thiamine, riboflavin, and niacin, and possibly two others, pyridoxine and pantothenic acid, are components of certain enzymes. Thus riboflavin is a constituent of the yellow enzyme of Warburg, thiamine of carboxylase, and niacin of certain dehydrogenases. When these are deficient in quantity or are absent, the orderly process of oxidation is interrupted and profound disease syn-

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347. Gordon, E. S. and Sevringhaus, E. L.: Vitamin Therapy in General Practice. Chicago: Year Book Publ., 1942.

dromes such as pellagra and beriberi are initiated. Vitamin deficiency diseases must, therefore, be considered essentially as metabolic disturbances due to interference with metabolic processes in the tissues.

It must be emphasized that inadequacy of aliments containing a given vitamin, e.g., vitamin A, is not the only means by which a deficiency results. Avitaminosis may well occur on a diet that is adequate enough in every respect. Table 44 presents a summary of the factors predisposing to the development of vitamin deficiency diseases. The importance of the conditioning factors cannot be overestimated.

In the early days of vitamin therapy there was a tendency to regard the few recognized vitamins as specific for definite ailments. Subsequent research, however, has led to the conclusion that a number of factors are generally involved in any nutritional deficiency and that nearly all avitaminoses in man represent mixed deficiency states. This was not established until the various vitamin factors had been isolated and synthetically produced in pure form and thus made available for experimental work. Outside of the experimental laboratory one rarely encounters a deficiency of one vitamin alone. Pellagra patients, for example, have often been found to show deficiencies of vitamins A, B_1, B_2, and C as well as niacin (Smith[348]).

Some important interrelationships among the vitamins are just beginning to be revealed. Thus, it is now recognized that the absorption, metabolism, and excretion of one factor may be conditioned in part by the nutritional status of the organism relative to various other and perhaps all other nutrients (Gordon and Sevringhaus[347]).

From Table 44 it can be seen that if malabsorption is the cause of a vitamin deficiency the physician will not be able to correct it by simply giving large doses of vitamins orally but will have to resort to parenteral administration. Moreover, if a patient has malutilization any vitamin therapy is futile until the underlying metabolic disturbance is corrected. In short, the diagnosis of a vitamin deficiency requires establishment of its fundamental pathogenesis in each case.

It now seems to be definitely established that many of the vitamins and minerals are interdependent. This is perhaps best exemplified by the well known interaction between calcium, phosphorus, and vitamin D. Moreover, recent experiments have suggested the probability of a relationship between vitamin C and protein, vitamin C and iron, vitamin C and calcium, thiamine and magnesium, and so forth.

It is becoming increasingly apparent that the body cannot be regarded as truly well nourished unless it receives every one of the essential food factors. Deficiency in one factor may impair absorption of another, thereby bringing deficiency in a third, and thus upsetting the whole delicate balance of the nutritional process. The most reliable guarantee against a weakness in any of the links of the nutritional chain would seem to be a balanced supplement of vitamins and minerals.

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[348] Smith, D. T.: M. Clin. North America 27: 379, 1943.

Table 44.—*Factors Predisposing to the Development of Vitamin Deficiency Diseases*

1. Inadequate intake of vitamins as a result of:
    a. Economic difficulties
    b. Inadequate available supplies (prisons, remote rural districts, shipboard)
    c. Devitaminization of foods (by storage, preserving methods, refining, milling, cooking)
    d. Ignorance of what constitutes an adequate diet
    e. Vagaries of taste, preference, and habit, including the eccentric, the food cultist, the psychoneurotic
    f. Alcoholism with low food intake
    g. Illness, by way of low total food intake
    h. Long-continued use of a therapeutic diet which is nutritionally inadequate
    i. Anorexia, dysphagia, dyspepsia, and pain

2. Poor absorption and utilization due to:
    a. Loss of food or of essential secretions
        (1) vomiting
        (2) diarrhea
        (3) external fistula
    b. Lack or diminished production of essential endogenous substances (anacidity, achylia)
    c. Inadequate intestinal absorption
        (1) obstructing gastro-intestinal lesions
        (2) atrophy or disease of the small intestine
        (3) internal intestinal or pancreatic fistulas
        (4) excessive use of mineral oil
    d. Alterations in metabolism

3. Increased need for vitamins which occur during periods of
    a. rapid growth (infancy and childhood)
    b. Pregnancy and lactation
    c. Increased metabolic activity, as in hyperthyroidism or increased muscular work
    d. Acute and chronic infections
    e. Personal high requirements in some individuals

4. Impaired metabolism or synthesis of the vitamins
    a. Due to disease of liver
    b. Due to faulty intestinal flora

The incidence of mild or subclinical deficiencies is much higher than has been supposed. Such conditions are now recognized as being just as important as any complete, pathologic deficiency disorder. Since they are less obvious they are, of course, more likely to pass unnoticed and far more difficult to detect.

Generally speaking, there are four methods of diagnosing dietary deficiencies: (1) by the signs and symptoms of a deficiency, as determined by history and physical examination; (2) analysis of the diet; (3) laboratory tests; and (4) a therapeutic trial.

TABLE 45.—*Recommended Daily Vitamin Allowances*[349]

	A U.S.P. Units	Thiamine B_1 mgm.	Riboflavin B_2 mgm.	Nicotinic Acid mgm.	Ascorbic Acid (C) mgm.	D* U.S.P. Units
Man (70 Kg.)						
Moderately active	5,000	1.8	2.7	18	75	
Very active	5,000	2.3	3.3	23	75	
Sedentary	5,000	1.5	2.2	15	75	
Woman						
Moderately active	5,000	1.5	2.2	15	70	
Very active	5,000	1.8	2.7	18	70	
Sedentary	5,000	1.2	1.8	12	70	
Pregnancy (latter half)	6,000	1.8	2.5	18	100	400–800
Lactation	8,000	2.3	3.0	23	150	400–800
Children up to 12 yrs.						
Under 1 yr.	1,500	0.4	0.6	4	30	400–800
1–3 yrs.	2,000	0.6	0.9	6	35	
4–6 yrs.	2,500	0.8	1.2	8	50	
7–9 yrs.	3,500	1.0	1.5	10	60	
10–12 yrs.	4,500	1.2	1.8	12	75	
Children over 12 yrs.						
Girls—13–15 yrs.	5,000	1.4	2.0	14	80	
16–20 yrs.	5,000	1.2	1.8	12	80	
Boys—13–15 yrs.	5,000	1.6	2.4	16	90	
16–20 yrs.	6,000	2.0	3.0	20	100	

* Vitamin D is undoubtedly necessary for older children and adults. When not available from sunshine, it should be provided probably up to the minimal amounts recommended for infants.

Needs of infants increase from month to month. The amounts given are for approximately 6 to 18 months. Allowances for children are based on the middle age for each group and for moderate activity.

Laboratory procedures and instruments for the assessment of the nutritional status have been vastly improved during the past few years. How-

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349. National Nutrition Conference. Washington, D. C., May 26–28, 1941.

ever, they are, on the whole, too complicated to be employed by anyone but a qualified biochemist or in special laboratories.

The vitamin requirements of a healthy individual as recommended by the Food and Nutrition Board of the National Research Council will be found in Table 45. Undoubtedly, the ideal situation would be to fill these requirements in the most natural manner, namely, by supplying all the necessary food elements. Consequently, it is of prime importance to acquire a thorough knowledge of the vitamin content of common foods and of the manner in which the vitamins are affected by processing, storing, and cooking. Detailed information on these points will be found in Part Five (p. 597). In pathologic cases, however, larger than normal doses of vitamins are often indicated. Table 46 gives the daily dosages required for specific vitamin deficiencies.

There is still a great deal of confusion about the method of expressing the potency of the vitamins. Those which are synthetically prepared are expressed in actual weight (metric). Others, however, are still estimated by biologic assay methods. Some vitamins are converted into so-called units, preceded by the name of the investigator. Fortunately, the international unit (I.U.) and the United States Pharmacopeia unit (U.S.P. unit) are identical. Table 47 gives a concise picture of the relationship between the more common expressions of vitamin potency. When expressed in weight, the metric system is always used, the denominations being grams, milligrams, and micrograms. The latter, one one-thousandth of a milligram, is often termed a gamma or micromilligram.

TABLE 46.—*Daily Dosages of Vitamins for Specific Deficiencies (Jolliffe & Smith*[341]*)*

Deficiency	Mild	Moderate	Severe
Vitamin A	100,000 U. (m)	200,000 U. (m)	200,000 U. (m)
Vitamin D	2,000 U. (m)	2,000 U. (m)	2,000 U. (m)
Thiamine	10–30 mg. (p)	20–50 mg. (p)	50–300 mg. (p)
Riboflavin	10 mg. (m)	10–20 mg. (m)	20–50 mg. (m)
Nicotinic acid and nicotinamide	300–500 mg. (m)	500–1,000 mg. (m)	1,000 mg. (m)
Ascorbic acid	500 mg. (m)	500–1,000 mg. (m)	1,000–2,000 mg. (m) 500 mg. (p)

(m) = by mouth. (p) = parenterally.

As mentioned above, a given dietary deficiency can rarely be specifically attributed to a deficiency of one vitamin alone. Therefore, when endeavoring to correct avitaminosis therapeutically, every effort must be made to regulate the dosage in such a manner as to provide the proper balance among the vitamins. Spies[350] advocates a basic formula containing 10 mg. of thiamine, 50 mg. of niacin, 5 mg. of riboflavin, and 75 mg. of ascorbic acid. When the symptoms of one deficiency disease are clearly predominant, he supplements the basic formula with additional amounts of the vitamin indicated for the dominant deficiency: for example, in the case of beriberi 10 mg. of thiamine daily, in riboflavin deficiency 5 mg. of riboflavin daily, in scurvy 100 mg. of ascorbic acid three times daily, and in mild pellagra 50 mg. of niacinamide twice daily. If the pellagra is severe the patient is given 150 mg. of niacinamide three times daily in addition to the basic formula. Diseases arising from a B-complex deficiency generally respond promptly to dried brewers' yeast powder, liver extract, wheat germ, and rice polishings. These substances are particularly valuable in that they contain appreciable amounts of protein and other essential nutrients, and probably also hitherto unidentified vitamins of the B complex.

TABLE 47.—*Vitamin Unit Equivalents* (*H. T. Kelly*[351])

Vitamin	Unit	Equals	Biologic Effect of
A	U.S.P. or I.U.	=	0.6 micromilligrams beta carotene or equivalent reference cod liver oil
B_1	U.S.P. or I.U.	=	3.0 micromilligrams thiamine chloride
B_2	Sherman-Bourquin	=	2.5 micromilligrams riboflavin
Nicotinic acid (niacin) amide	None	Potency stated in milligrams of pure chemical	
Pantothenic acid (filtrate factor)	Jukes-Lepkowski	=	14 micromilligrams pantothenic acid
B_6	None	Potency stated in milligrams of pure chemical	
C	U.S.P. or I.U.	=	50 micromilligrams ascorbic acid
D	U.S.P. or I.U.	=	1 milligram reference solution ergosterol or 0.025 micromilligrams, crystalline vitamin D
E	Evans-Burr	=	Approximately 2 milligrams alpha tocopherol
Menadione (K)	None	Potency stated in milligrams of pure chemical	

The daily dose of dried brewers' yeast powder or oral liver extract is

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350. Spies, T. D.: M. Clin. North America 27: 273, 1943.
351. Kelly, H. T.: Pennsylvania M. J. 46: 961, 1943.

120 Gm. (4 oz.) and of wheat germ and of rice polishings 150 Gm. (5 oz.).

In addition to this specific vitamin therapy, a diet rich in calories and proteins is indicated.

Before considering the relationship between various vitamins and the skin, a few additional remarks of a general character should be made. As will be shown in some detail, the skin is a valuable guide in the recognition and diagnosis of nutritional deficiencies. It is noteworthy that in animal experiments, of all the various organs of the body the skin and its appendages have been found to exhibit the greatest evidence of vitamin deficiency, particularly if the diet is deficient in vitamins A, B_2, B_6, niacin, and C. The fact that the epidermis can regenerate as speedily as it does may possibly explain this tissue's exceptional requirements for these substances and its relatively early involvement when they are lacking. It should be borne in mind, however, that most of the reports on this subject refer to studies performed on experimental animals. While some of the findings are applicable to man, most of them are not. Nevertheless we should like to make special mention of the very important contributions of Sullivan and his collaborators, Nicholls[352–358] and Evans[359–361] on the nutritional dermatoses in rats which we shall have occasion to cite repeatedly in the following pages.

Dermatoses caused by vitamin deficiencies may be divided into two groups: (1) true (or obligatory) and (2) relative (or facultative). The classification depends on whether the vitamin factor represents the decisive pathogenetic element in the dermatosis or is one of the essential elements in the pathogenetic chain, or whether it plays a partial but not the decisive role.

In addition, it is important to note that involvement of large areas of skin by a dermatologic disturbance for a long period of time may lead to avitaminosis. Thus McNee[362] and Marchionini[363] have demonstrated that widespread cutaneous manifestations, such as extensive dermatitis,

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352. Sullivan, M. and Nicholls, J.: J. Invest. Dermat. **3:** 309, 1940.
353. Sullivan, M. and Nicholls, J.: J. Invest. Dermat. **3:** 337, 1940.
354. Sullivan, M. and Nicholls, J.: J. Invest. Dermat. **4:** 123, 1941.
355. Sullivan, M. and Nicholls, J.: J. Invest. Dermat. **4:** 181, 1941.
356. Sullivan, M. and Nicholls, J.: Arch. Dermat. & Syph. **45:** 295, 1942.
357. Sullivan, M. and Nicholls, J.: Arch. Dermat. & Syph. **45:** 917, 1942.
358. Sullivan, M., Kolb, L. C., and Nicholls, J.: Bull. Johns Hopkins Hosp. **70:** 177, 1942
359. Sullivan, M. and Evans, V. J.: J. Nutrition **25:** 319, 1943.
360. Sullivan, M. and Evans, V. J.: J. Nutrition **27:** 123, 1944.
361. Sullivan, M. and Evans, V. J.: Arch. Dermat. & Syph. **51:** 17, 1945.
362. McNee, J. W.: Brit. J. Dermat. **54:** 159, 1942.
363. Marchionini, A. and Patel, C.: Arch. f. Dermat. u. Syph. **175:** 419, 1937.

psoriasis, or severe generalized sunburn, bring about a decline in the vitamin A level in the blood. They attribute this to a temporary impairment of the liver function.

I. VITAMIN A DEFICIENCY

Vitamin A, which has as yet no other official designation despite the fact that its structural formula is well known, is a fat-soluble, unsaturated alcohol. It occurs in esterified form in the blood and in the storage depots. Vitamin A is found in foods of animal origin such as the liver oils of cod, halibut, and certain other fishes, mammalian livers, egg yolk, cream cheese, butter, cream, and milk. Carotene, in its alpha, beta, and gamma forms, and another carotenoid, cryptoxanthin, present in plants, are known to, be precursors of vitamin A and are changed into this vitamin in the animal body, apparently in the liver. Carotene is abundantly found in thin-leaved green plants such as beet, kale, chard, spinach, turnip; also in carrots, squash, sweet potato, pumpkin, apricot. Cryptoxanthin is found in yellow corn and egg yolk. The unit of vitamin A is the amount necessary to produce the physiologic effect of 0.6 micrograms of pure beta carotene.

The factors predisposing to vitamin A deficiency are:

(1) *Inadequate intake.* This may be due to poverty, self-imposed or therapeutic dietary restrictions, oxidation of vitamin A by prolonged cooking and heating of foods, or seasonal diminution of vitamin A in foods.

(2) *Inadequate absorption.* A normal amount of fat or bile must be present to insure the absorption of vitamin A from the small intestine; hence, any disease which causes diminished flow of bile or interferes with fat digestion will hinder the absorption of vitamin A and its provitamin. With fat-free diets, the carotene absorption is reduced by one half. Excessive use of mineral oil may also prevent absorption of carotene.

(3) *Inadequate utilization.* The ability of the liver, the most important storage organ of vitamin A, to store this vitamin is impaired in hepatic cirrhosis. This is chiefly due to altered intermediary metabolism of vitamin A in the liver. Moreover, patients with diabetes have difficulty in converting carotene to vitamin A, which accounts for the carotenemia so often seen in diabetics. This, too is in all probability due to impairment of liver function. Finally, vitamin A is not utilized properly in hypothyroidism.

(4) *Increased requirements.* These occur in infections and in pregnancy.

Sulzberger[364] proposed the term "dysvitaminosis" for vitamin deficiencies which are caused by abnormal conditions of demand, utilization, and transport of vitamins, in contradistinction to those cases which are due to simple dietary deficiency and which are appropriately called hypovitaminoses or avitaminoses.

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[364] SULZBERGER, M. B. and COPE, E. P.: J. Lab. & Clin. Med. 26: 1403, 1941.

The daily vitamin A requirements as recommended by the Food and Nutrition Board, National Research Council are: infants 1,500, children 4,500, adolescents and adults 5,000, and pregnant or lactating women 6,000 to 8,000 units. In acute deficiencies 35,000 to 200,000 units per day are needed.

Clinical Manifestations of Vitamin A Deficiency Other Than in the Skin

Severe avitaminosis A of the skin is generally accompanied by characteristic changes in other ectodermal structures. Familiarity with such symptoms and signs is essential for the early recognition of cutaneous vitamin A deficiency and these are therefore presented in brief.

In addition to hyperkeratosis of the skin, which is discussed below, the outstanding results of avitaminosis A are night blindness, malformation of teeth, atrophy and keratinization of epithelial tissues, which may manifest themselves as conjunctivitis, xerophthalmia, keratomalacia, and keratinizing metaplasia of the mucous membranes of the respiratory, alimentary, and genito-urinary tracts.

Eyes: Night blindness (nyctalopia) is the loss of visual acuity in dim light. Perception of light depends on an adequate supply of visual purple, of which vitamin A is a constituent. When a deficiency of vitamin A exists, the visual purple is not formed as fast as it is broken down under the influence of light. Night blindness is an early sign of vitamin A deficiency.

Another evidence of avitaminosis A are the so-called Bitot spots, consisting of circumscribed areas of xerosis of the conjunctiva situated laterally to the cornea and sometimes forming well defined white spots (Fig. 37).

Xerophthalmia and keratomalacia result from severe vitamin A deficiency. Xerophthalmia, or dryness of the conjunctiva, is characterized by decreased secretion of tears, loss of eye luster, areas of patchy dryness, and thickening and wrinkling of the conjunctiva. Keratomalacia, or corneal softening, occurs in the final stages. Although xerophthalmia and keratomalacia are rare in the United States, they may occur in epidemic proportions in periods of war and famine.

Teeth: Vitamin A deficiency produces atrophy and metaplasia of the enamel-forming organs of the teeth (ameloblasts). The enamel may be structurally defective, containing pits and fissures which predispose to decay or, in severe deficiencies, may be completely lacking. Diminished and defective formation of dentin likewise occurs, causing striking deformities of the teeth.

Respiratory tract: Any part of the respiratory tract may undergo keratinizing metaplasia. Clinical effects associated with epithelial atrophy may occur long before keratinization is noted. In infants the trachea and bronchi may be affected early in vitamin A deficiency. This explains the frequency, severity, and persistence of pneumonia, which so often causes death in infants receiving insufficient vitamin A. Such pneumonias are commonly of the interstitial or peribronchial type.

Gastrointestinal Tract: Lesions of the gastrointestinal tract are rare although the esophagus undergoes characteristic hyperkeratinization.

Genitourinary Tract: Keratinization of the renal pelvis and ureters of infants commonly occurs, being next in frequency to respiratory tract damage.

The question whether vitamin A may act as an "anti-infective vitamin" is highly controversial. However, recent well controlled studies on human subjects have failed to reveal any relationship between known quantitative immunologic reactions and prolonged periods of vitamin A depletion (Gordon and Sevringhaus[317]). In experimental animals Sternberg and Pillsbury[365] demonstrated that this vitamin played no role in preventing or curing pyogenic infections of the skin.

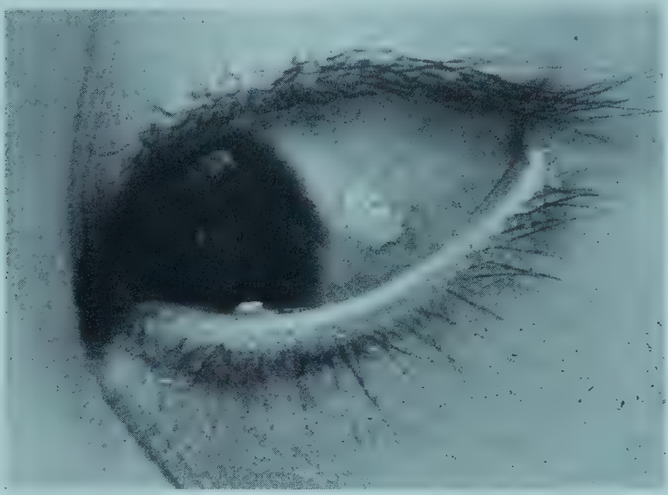

FIG. 37. BITOT SPOT ON THE CONJUNCTIVA IN A CASE OF SEVERE VITAMIN A DEFICIENCY

(Courtesy of Dr. P. Fasal and the Archives of Dermatology and Syphilology.)

Another condition which has been shown to be due to vitamin A deficiency is the Sjögren[366] syndrome, which is characterized by marked dryness of the conjunctiva and the mucous membranes of the upper respiratory tract and the stomach. These appear as reduced lacrimation and keratoconjunctivitis sicca; xerostoma; rhinitis; pharyngitis; laryngitis; tracheitis; bronchitis sicca; and achylia gastrica. For details see page 460.

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[365] STERNBERG, T. H. and PILLSBURY, D. M.: Arch. Dermat. & Syph. **35:** 247, 1937.

[366] SJÖGREN, H.: Acta ophth. (Copenhagen) **10:** suppl. ii, 1932; **13:** 1, 1935.

Cutaneous Manifestations of Vitamin A Deficiency

The cutaneous manifestations of vitamin A deficiency in man were first systematically studied by Pillat,[367] Frazier and Hu[368] and Reiss,[369] in China, Loewenthal[370] in Africa, Nicholls[371] in Ceylon, Akroyed and Rajagopal[372] and Rao[373] in India, and Fasal[374] in Malaya. Youmans and Corlette[375] and Lehman and Rapaport[375a] reported the first cases in the United States. The specific pathologic changes in the skin resulting from vitamin A deficiency are directly due to epithelial metaplasia. The normal epithelium becomes atrophic and is replaced by proliferating basal cells which become keratinized. In the early stages, dryness and roughness of the skin are the only signs; these are caused by hyperkeratosis and parakeratosis of the epidermis and by hypofunction of the sebaceous and sweat glands due to hyperkeratinization of the lining epithelium of these glands, which ultimately results in their atrophy. (In infants, vitamin A deficiency leads to an atrophied stage which is characterized by thinning of the epidermis [Frazier et al.[376]]) When the dryness is mild, it is often more readily detected by palpation than by inspection. The next stage resembles an exaggerated state of gooseflesh. The more advanced cases are characterized by hyperkeratotic follicular lesions appearing at the sites of the pilosebaceous follicles, principally on the anterolateral aspects of the thighs (Fig. 38) and on the posterolateral aspects of the upper arms and forearms. The eruption may then spread to the shoulders, back, buttocks, abdomen, and, in some exceptional cases, to the face and posterior aspect of the neck as well. The hands and feet are never involved. These lesions vary from filiform processes (Fig. 39) to small, conical papules with a central intrafollicular plug (Fig. 40) which projects from the surface or is covered with a loosely aderent scale or contains a broken-off or coiled, unerupted hair. When the follicular keratoses are pronounced, they give the skin a rough, grater-like feel, whence the term "nutmeg-grater skin" (Stannus[377]). Last of the pathologic changes to appear are the broad, flat papules, each with a massive horny central plug, which may fall out, leaving a wide crater. Since the pattern of these large, flat papules is somewhat reminiscent of

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367. Pillat, A.: Chinese M. J. **43:** 907, 1929.
368. Frazier, C. N. and Hu, C. K.: Arch. Int. Med. **48:** 507, 1931.
369. Reiss, F.: Chinese M. J. **50:** 945, 1936.
370. Loewenthal, L. J. A.: Arch. Dermat. & Syph. **28:** 700, 1933.
371. Nicholls, L.: Indian M. Gaz. **68:** 681, 1933.
372. Akroyed, W. R. and Rajagopal, K.: Indian J. M. Research **24:** 419, 1936.
373. Radhakrishna Rao, M. V.: Indian J. M. Research **24:** 727, 1937.
374. Fasal, P.: Arch. Dermat. & Syph. **50:** 160, 1944.
375. Youmans, J. B. and Corlette, M. B.: Am. J. M. Sc. **195:** 644, 1938.
375a. Lehman, E., and Rapaport, H. G.: J.A.M.A. **114:** 386, 1940.
376. Frazier, C. N., Hu, C. K., and Chu, F. T.: Arch. Dermat. & Syph. **48:** 1, 1943.
377. Stannus, H. S.: Practitioner **146:** 303, 1941.

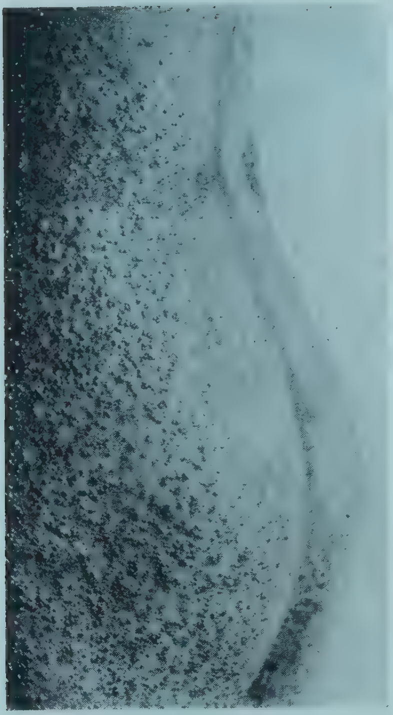

Fig. 38. Phrynoderma

Diffuse involvement of hair follicles due to vitamin A deficiency.
(Courtesy of Dr. C. N. Frazier and the Archives of Dermatology and Syphilology.)

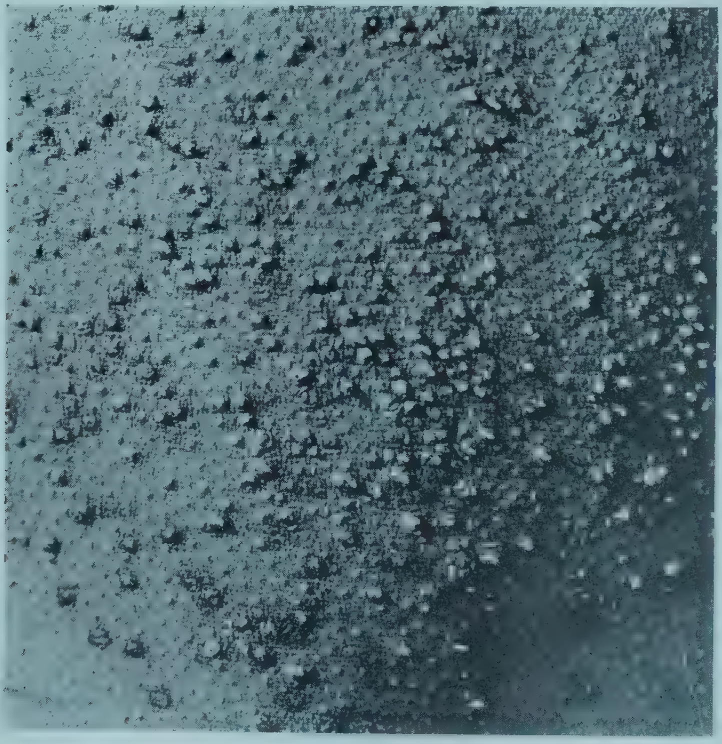

Fig. 39. Follicular Hyperkeratosis

Filiform horny spines in a youth with vitamin A deficiency.
(Courtesy of Dr. C. N. Frazier and the Archives of Dermatology and Syphilology.)

"toadskin," Nicholls[371] gave this condition the now generally accepted name of "phrynoderma." The papules are generally from 1 to 2 mm. in diameter, but they may become as large as 5 mm. in diameter in especially severe cases. The consistency of the papules is firm; their color is either the same as that of the surrounding skin or, more commonly, slaty brown. The normal surface markings are exaggerated here and there, giving the skin a finely wrinkled appearance. Dryness of the scalp is common. Sweating is often conspicuously absent.

Follicular lesions of another type are those found on the face and, in Loewenthal's Negro material,[370] also on the chest and back. These lesions are hemispherical in contour, a few millimeters in diameter, generally pigmented, and covered by a loosely adherent scale. They resemble comedones (Fig. 41); however, unlike the typical comedones of acne, they are dry and nonsuppurative (Loewenthal[370]).

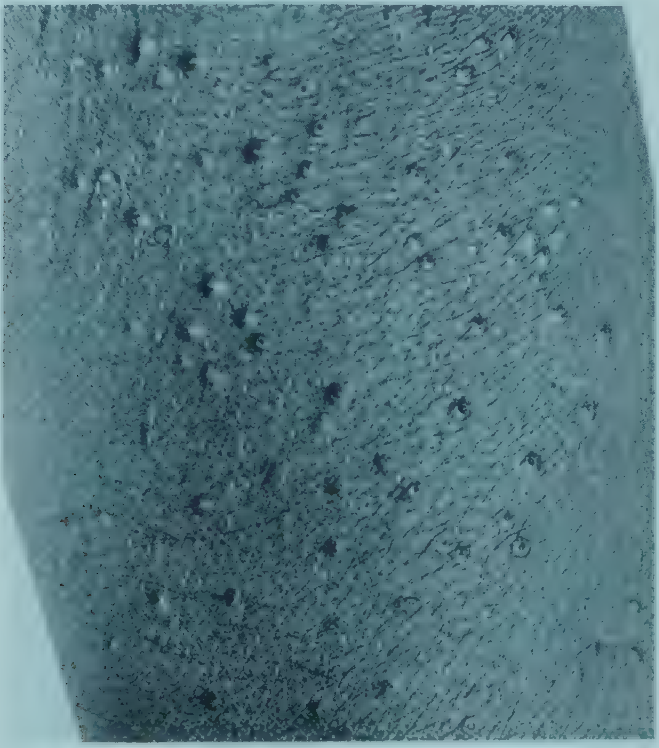

FIG. 40. FOLLICULAR HYPERKERATOSIS

Conical papules with central horny spines.
(Courtesy of Dr. P. Fasal and the Archives of Dermatology and Syphilology.)

In advanced stages, the skin may assume an ichthyotic appearance (Fasal[374]). However, as Fasal has pointed out, it is possible to differentiate between a true ichthyosis and an ichthyotic condition due to vitamin A deficiency, for the former affects the palms and soles, while this localization has never been observed in the latter condition.

In some cases, wartlike plaques of hyperkeratosis are seen on the ankles, knuckles, and heels (Stannus[377]).

Subjective symptoms such as itching may occur (Lehman and Rapaport,[376] Loewenthal[370]), and they may at times be extremely severe (Jeghers[322]).

Noteworthy, too, are the changes in the color of the skin. The normal pinkish color fades and becomes sallow or ashen gray, in children and adults alike, and the change in the color becomes more and more pronounced the longer the vitamin A deficiency lasts. It shows first on the face, which may assume an appearance similar to that of chloasma uterinum subsequently, the extensor aspects of the forearms and legs, as well as the chest, become affected (Pillat[378]). In some patients, the skin in general has a dull, slaty color. Tolmach and Graham[379] observed a case presenting innumerable perifollicular deposits of pigment. After ten weeks of

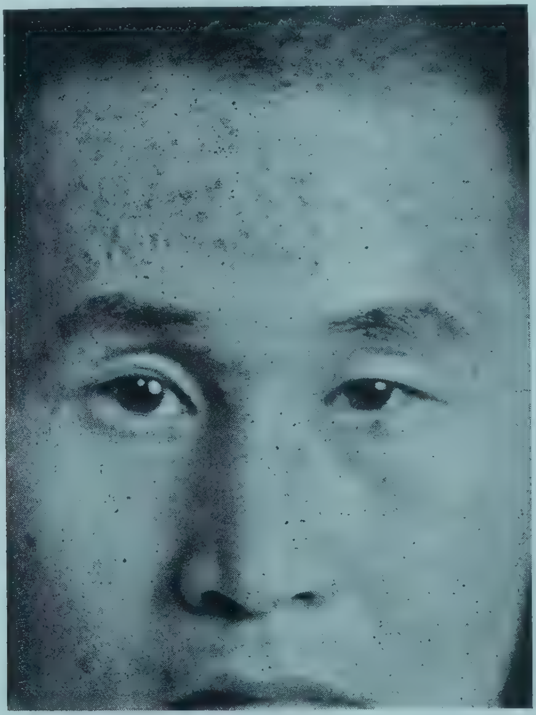

Fig. 41. Comedo-like Lesions on the Forehead in a Patient with Vitamin A Deficiency

This eruption disappeared on administration on a diet high in vitamin A. (Courtesy of Dr. F. Reiss.)

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378. Pillat, A.: Ernährungslehre, edited by Stepp, W. Berlin: Springer, 1939.
379. Tolmach, J. A. and Graham, T. N.: Arch. Dermat. & Syph. 45: 1156, 1942.

treatment with high doses of vitamin A, pigmentation had been reduced about 50 per cent. Loewenthal[370,380] reports that the skin of the Uganda natives changes from a lustrous to a dull grayish black, especially on the extensor sides of the extremities, on the hips, and in the gluteal zone.

This alteration in the color of the skin is attributable, first, to the fact that the epithelium becomes less and less transparent as the disease continues, with the result that the blood vessels of the corium cannot give the skin its normal pinkish color. This is due to the multiplication of the cellular layers in the epithelium and, at the same time, the progressive dehydration of the epithelial cells and the accelerated cornification (Pillat[378]). Another reason for the change in the color of the skin is the increase in pigmentation. By means of Bloch's dopa reaction, Mu, Frazier, and Pillat[381] succeeded in demonstrating the presence of abnormally great amounts of melanin in the skin of individuals suffering vitamin A deficiency.

Changes in the hair and nails may be observed in cases of severe avitaminosis A. According to Pillat,[378] the changes in the hair may be listed in the following order, depending on the severity of the case: first, the hair loses its sheen and luster, and shows signs of dryness; then, if the avitaminosis becomes more pronounced, the hair begins to fall out or to blanch. These changes are apparently caused by atrophy of the hair bulbs and by cystic degeneration of some of them. Changes in the coats of animals (rats, rabbits) have been described by Gudjonssen,[382] Moult,[383] Sullivan and Evans,[361] Josephs,[321] and other investigators. The literature also contains some reports of changes in the nails (White,[384] Reiss,[369] Pillat[378]), including dullness, dryness, and brittleness as well as punctate pitting, transverse furrows, and longitudinal ridges. Small horny scales can readily be removed from the surface of the nails.

Although the epidermis very quickly manifests the effects of a vitamin A deficiency, the epithelial layers of the skin do not contain this vitamin. The most accurate investigative procedure available, fluorescence microscopy, fails to disclose the presence of any trace of vitamin A in this tissue even after its administration in massive doses (Cornbleet and Popper,[385] Popper[386]). Small amounts of vitamin A can be observed only in the fat cells of the cutis and subcutis. Moreover, Cornbleet and his collaborators[387] investigated the vitamin A and carotene levels in the plasma of

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380. Loewenthal, L. J. A.: Ann. Trop. Med. **29:** 407, 1935.
381. Mu, J. W., Frazier, C. N., and Pillat, A.: Chinese J. Physiol. **11:** 247, 1937.
382. Gudjonssen, S. V.: Acta ophth. (Copenhagen) **8:** 184, 1930.
383. Moult, F. H.: Arch. Dermat. & Syph. **47:** 768, 1943.
384. White, C.: J. A. M. A. **102:** 2178, 1934.
385. Cornbleet, T. and Popper, H.: Arch. Dermat. & Syph. **46:** 59, 1942.
386. Popper, H.: Physiol. Rev. **24:** 205, 1944.
387. Cornbleet, T., Popper, H., and Steigmann, F.: Arch. Dermat. & Syph. **49:** 103, 1944.

fifty-five patients with various dermatologic diseases and found no characteristic deviations from the levels of hospital controls.

We do not as yet know just how the epidermis is affected by avitaminosis A. The mechanism involved is probably highly complex.

Histopathology: The principal microscopic changes of the skin in vitamin A deficiency consist of a superficial hyperkeratosis of the epidermis extending into the mouths of the pilosebaceous follicles. Subsequently, this follicular hyperkeratosis becomes so pronounced that the orifices may become partly distended by a bulbous mass of keratin (Fig. 42), although the hair continues to grow and the sebaceous glands may remain normal. If the keratinization progresses further, the follicular orifices become widely distended (Fig. 43) and the growth of hair and the outflow of sebum are definitely impeded. Eventually this process leads to the formation of a distinct plug consisting of a stratified mass of keratin; the hair follicles then become completely disorganized and the attached sebaceous glands atrophy (Fig. 44). Steffens and associates[388] succeeded in producing experimentally the microscopic cutaneous lesions of vitamin A deficiency in a healthy human subject; and Moult,[383] Sullivan and Evans,[361] and others have induced keratotic plugs in the hair follicles of rats. Moult points out, however, that cessation of hair growth and atrophy of individual sebaceous glands are caused, primarily, by the mechanical obstruction presented by the keratotic plugs that fill the hair follicles (Figs. 45, 46, 47).

On the basis of the clinical and histopathologic similarity between these dermatologic lesions and other dermatoses characterized by follicular hyperkeratosis, it has been claimed that keratosis pilaris, lichen pilaris, lichen spinulosus, and ichthyosis follicularis are merely descriptive terms for the same cutaneous manifestations of avitaminosis A. Moreover, there is some evidence that other hyperkeratotic, parakeratotic, and dyskeratotic conditions, such as keratosis follicularis (Darier's disease) pityriasis rubra pilaris, ichthyosis, dermatosis papillaris capilitii, callosities, keratoderma of the palms and soles, keratosis blennorrhagica, xeroderma pigmentosum, leukoplakia, and kraurosis vulvae may be caused, at least in part, by a disfunction in vitamin A absorption, transportation, and utilization.

This assumption is based on the clinical improvement which to some degree and for some time can be observed in the above-mentioned dermatoses after administration of high doses of vitamin A for several months. These favorable results do not in any way contradict the established nevoid hereditary character of many of these conditions, nor do they necessarily

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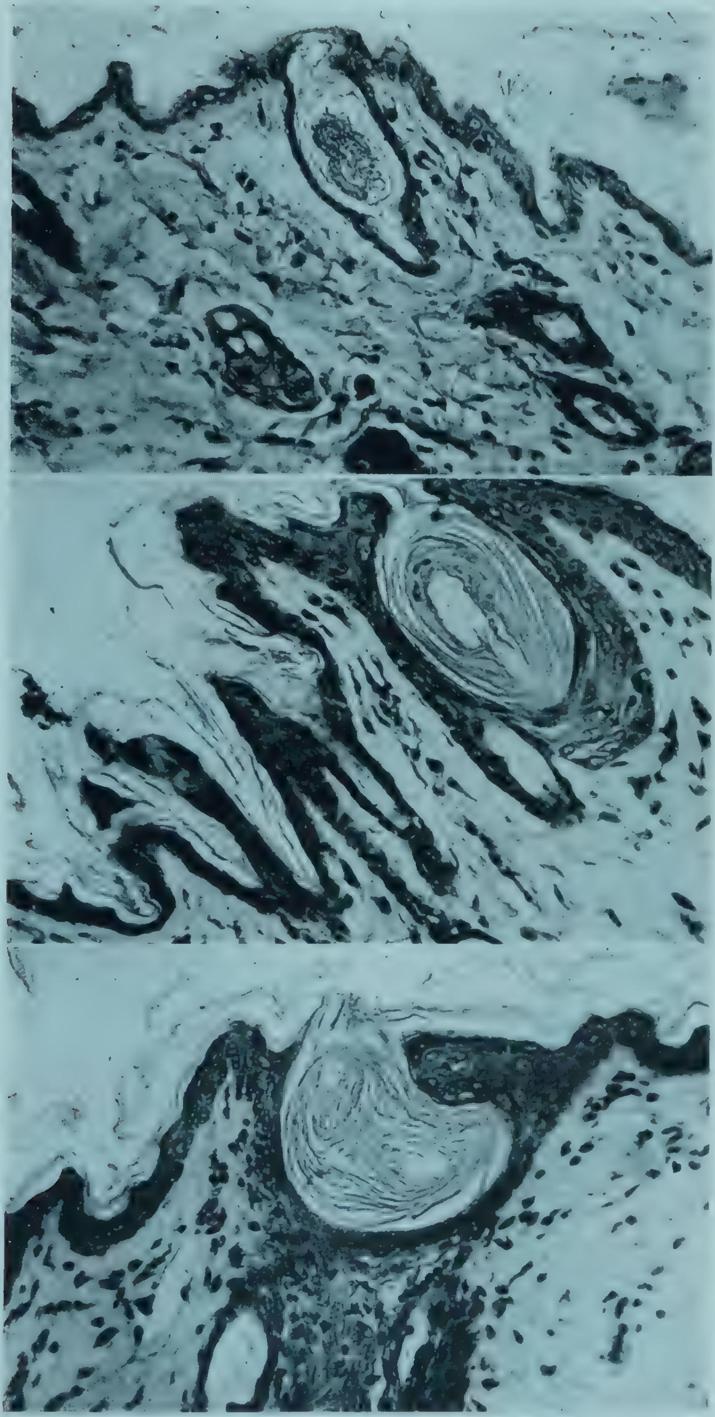
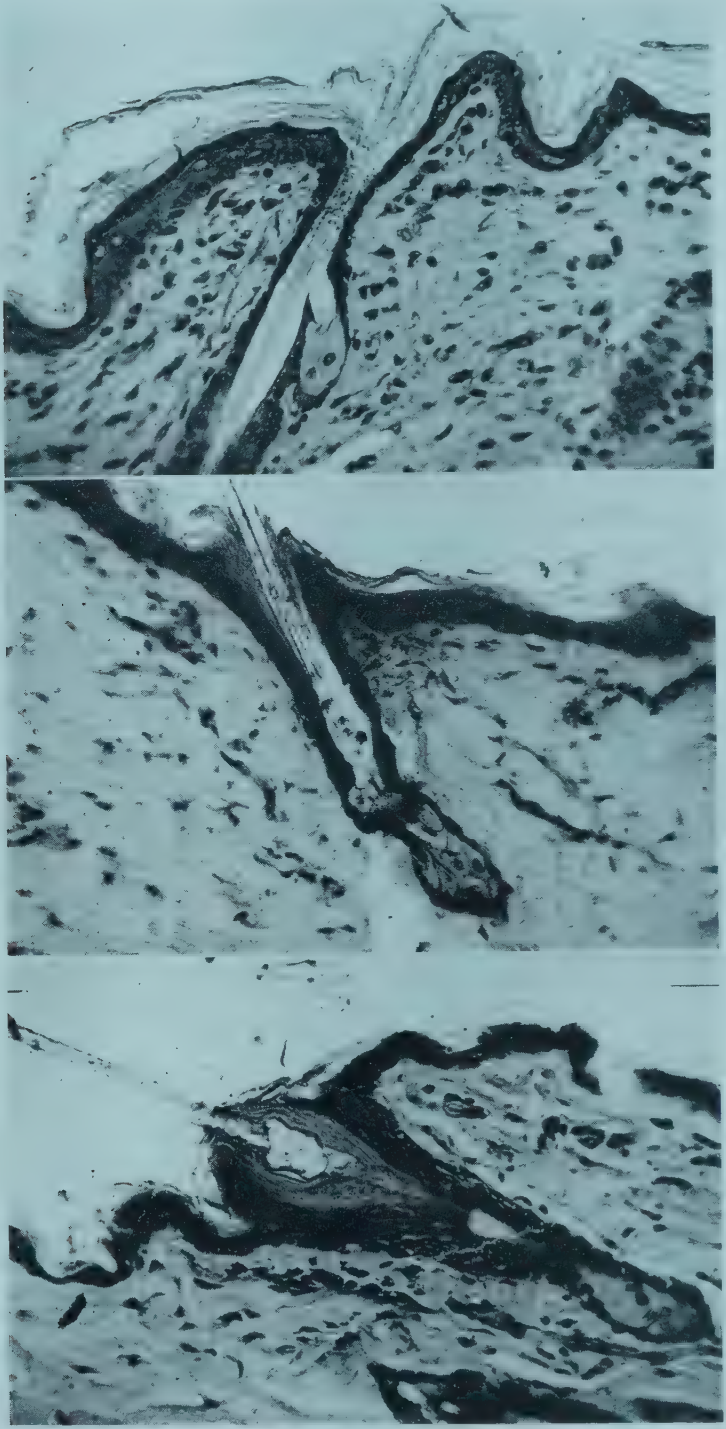
[388] Steffens, L. F., Bair, H. L., and Sheard, C.: Proc. Staff Meet., Mayo Clin. 14: 698, 1939.



Photomicrographs (× 250) of Sections of Skin from Rats Maintained from Birth on a Diet Deficient in Vitamin A

Fig. 42 (upper). Rat killed at the age of 23 days.
Fig. 43 (center). Rat killed at the age of 55 days.
Fig. 44 (lower). Rat killed at the age of 85 days.

Note the progressive keratinization and distention of the follicular orifice. (Courtesy of Dr. F. H. Moult and the Archives of Dermatology and Syphilology.)



PHOTOMICROGRAPHS (× 250) OF SECTIONS OF SKIN FROM RATS MAINTAINED FROM BIRTH ON A DIET DEFICIENT IN VITAMIN A

FIG. 45 (upper). Rat killed on the day of weaning.
FIG. 46 (center). Rat given 2 units of vitamin A daily for one month.
FIG. 47 (lower.) Rat given 2 units of vitamin A daily for two months.

Note the continued keratinization and distention of the upper third of each hair follicle.

(Courtesy of Dr. F. H. Moult and the Archives of Dermatology and Syphilology.)

indicate that these keratoses, dyskeratoses, or ichthyotic states are true vitamin A deficiencies (Wise and Sulzberger[390]).

Lastly, Straumfjord[391] claimed that vernix caseosa, in the newborn, is a manifestation of vitamin A deficiency representing disturbances in cornification.

These various skin conditions will be more fully discussed in Chapter XIV.

Diagnosis of Vitamin A Deficiency: The patient should be examined for the characteristic cutaneous symptoms and signs outlined above as well as for night blindness and xerosis of the cornea. However, the present consensus is that the dark adaptation test is not entirely dependable as a diagnostic index of vitamin A subnutrition. The dietary intake of vitamin A should be carefully investigated, and the physician should look for any possible interference with the normal absorption and utilization of fats, such as biliary obstruction, vomiting, diarrhea, tuberculosis, excessive use of mineral oil. Determination of the vitamin A and carotene levels in the blood may be helpful. While the various methods yield different values, 96 I.U. for women and 126 I.U. for men are satisfactory average figures. However, since vitamin A is stored in the body, vitamin A blood levels do not necessarily represent the state of depletion of the reserves, but rather reflect the balance between storage and utilization by the peripheral tissues. It has been observed that a relatively long period of depletion is required to produce an appreciable and sustained depression of the vitamin A level in the blood (Gordon and Sevringhaus[347]). Histologic findings are a helpful guide in cases with skin manifestations. Finally, a therapeutic test with large doses (100,000 U.S.P. units daily) administered over a reasonable length of time (about three months) may often be the only way to arrive at a definite conclusion.

Treatment: Dermatoses due to vitamin A deficiency generally respond slowly to therapy and usually require large doses (50,000 to 200,000 U.S.P. units per day) for months. Moreover, it may be necessary to continue giving large doses of vitamin A even for years in order to maintain the improvement. Thus, Peck et al.[392] reported that in three out of ten cases of keratosis follicularis (Darier's disease) the cutaneous lesions showed gradual improvement after some 200,000 U.S.P. units of vitamin A per day had been administered over a long period of time. The improvement in the skin was preceded by a restoration of normal vitamin A levels in the blood serum. When vitamin A therapy was discontinued, the skin manifestations gradually reappeared and the vitamin A content of the blood declined to its former low level, even when the diet included adequate amounts of vitamin A.

390. Wise, F. and Sulzberger, M. B.: The 1940 Year Book of Dermatology and Syphilology. Chicago: Year Book Publ., 1941.
391. Straumfjord, J. V.: West. J. Surg., 48: 341, 1940.
392. Peck, S. M., Glick, A. W., Sobotka, H. H., and Chargin, L.: Arch. Dermat. & Syph. 48: 17, 1943.

Oral therapy is not always efficacious; moreover, this mode of administration is sometimes difficult or impossible, as in the case of infants and some children. Here it is necessary to resort to the parenteral route. The latter mode of administration may also be preferable in patients requiring massive doses of the vitamin, in cases where the vitamin is not readily absorbed, or in those with liver damage which interferes with storage.

Vitamin A, even when given in doses as large as 300,000 units, rarely has toxic effects in man. Mild symptoms, such as a vague feeling of malaise, are occasionally encountered during the first days of treatment, but these symptoms soon disappear (Youmans[132]). More commonly encountered is an allergy to the fish oils from which this vitamin is derived. It is hoped that further purification and concentration of these preparations will overcome their allergenic properties. In the meantime, individuals who are hypersensitive to vitamin A or its menstruum will have to resort to carotene as a substitute.

Frazier and Li[393] treated patients presenting cutaneous lesions with daily injections of 1 to 2 mg. of carotene in oil and achieved results in fifty-one days. Fasal[374] found red palm oil, a carotene-rich product of the oil palm of Malaya, to be curative. Moreover, this oil was also found to be beneficial when applied locally.

It must be borne in mind, however, that treatment does not consist exclusively in administering vitamin A. Every effort should be made to identify and deal properly with any conditioning disease, such as a gastrointestinal disorder, hepatic disturbance or infection, which may hamper absorption and utilization of the vitamin.

Finally, one should never forget that single vitamin deficiency in man occurs only rarely. The addition of several vitamins and perhaps also an increase of protein intake and a well balanced diet are sometimes necessary for a satisfactory result, even though clinically only a vitamin A deficiency appears to exist.

II. VITAMIN B DEFICIENCIES

Vitamin B is the customary designation for a group of water-soluble vitamin factors. However, what was once referred to as vitamin B was found to consist of two distinct fractions: (1) a thermolabile, antineuritic factor (B_1); and (2) a thermostable antidermatitis factor (B_2). Subsequently both fractions were resolved into a number of component parts. Since these water-soluble fractions are found closely associated in nature and are most probably interdependent in their action, this group is now designated by the generic term "vitamin B complex." Most authorities today regard the following ten factors as members of the vitamin B complex: thiamine hydrochloride (B_1), riboflavin (B_2), pyridoxine (B_6), niacin,

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393. Frazier, C. N. and Li, H. C.: Chinese M. J. 54: 301, 1938.

pantothenic acid, biotin, inositol, choline, para-aminobenzoic acid, and adenylic acid. Furthermore, additional fractions which have not yet been identified have been shown to exist in yeast, liver, and rice bran. These have been described in terms of the biologic effects observed when a combination of the known and isolated constituents failed to produce a biologic response equivalent to that evoked by the yeast or liver or rice bran from which they were extracted. It is to be expected that as investigation in this direction continues still more members of the B complex will be isolated and identified, and that other fractions, formerly regarded as separate vitamins (such as B_3, B_4, and B_5), will be found to be identical with factors previously well defined.

TABLE 48.—*Constituents of the Vitamin B Complex*

Vitamin B: The entire B complex
Vitamin B_1: Thiamine hydrochloride (aneurin, antineuritic factor, antiberiberi factor)
Vitamin B_2: Riboflavin (vitamin G, lactoflavin)
Vitamins B_3, B_4, B_5: Have never been isolated; may be identical with other factors
Vitamin B_6: Pyridoxine (adermin, antidermititis factor for rats)
Niacin and niacinamide: nicotinic acid and nicotinic acid amide, P-P factor (pellagra preventive factor)
Pantothenic acid: Chick antidermititis factor, anti-gray hair factor in rats
Biotin: Vitamin H, co-enzyme R: anti-egg white injury factor
Inositol: Mouse anti-alopecia factor
Para-aminobenzoic acid: A hair-color factor for the rat and growth-promoting factor for the chick
Choline: Prevents fatty liver in the depancreatized dog
Adenylic acid: A constituent of co-enzymes I and II which catalyze cellular respiration
Folic acid: Vitamin B_c; chick anti-anemia factor
Filtrate factor: That fraction of the vitamin B complex remaining in the filtrate after removal of vitamins B_1, B_2, B_6, niacin, biotin, adenylic acid, and perhaps other factors from yeast or liver by their absorption on fuller's earth. Contains: pantothenic acid, para-aminobenzoic acid, choline, and possibly other unknown factors.

Table 48 presents a list of the accepted names of the various components of the vitamin B complex, together with their former or foreign designations.

Of all these factors, only those will be discussed here which are definitely pertinent to cutaneous pathology in man and in animals. To begin with, however, we shall consider the clinical importance of the entire B complex.

aa. Vitamin B Complex Deficiency

As mentioned above, it is known that the various members of the B complex are present in the same foods. Recent studies have shown that a deficiency of one of these vitamins is likely to be accompanied by a deficiency of other members of the group. Moreover, as Rynearson[394] and others have pointed out, a condition demonstrably due to the lack of one fraction alone is a rarity. This is strikingly illustrated by the situation in pellagra, where niacin or niacinamide must be supplemented by thiamine hydrochloride and riboflavin. But even these "big three" constituents of the B complex do not always suffice to relieve all the symptoms in pellagrins; in some instances, pyridoxine must also be administered before complete recovery can be achieved (Spies et al.[395]).

The vitamins of the B group are essential to the oxidation-reduction mechanism of all living cells because they serve as the prosthetic or chemically active group in the co-enzyme systems involved in that mechanism. When there is an inadequate supply of these substances, cellular metabolism is impaired and, in the course of time, functional and subsequently organic changes make their appearance. The disordered cellular metabolism permits the accumulation of intermediary products of carbohydrate oxidation, such as pyruvic and lactic acids. There are thus two stages in deficiency diseases, the first being characterized by interference with physiologic function, the second by actual anatomic changes. Sufficient chemical and clinical evidence is available to prove that there is a close interrelationship between these vitamins and that functional impairment will result unless all are supplied in adequate amounts.

The very fact that deficiency of riboflavin and niacin can produce characteristic lesions of the skin and mucous membranes signifies that cutaneous eruptions can develop as a result of cellular disturbances which are due to an interference with the process of biologic oxidation and other enzymatic functions. It is fitting to mention here similar concepts formulated by Unna[396] twenty-five years ago on the basis of biologic-chemical investigations.

The richest natural source of vitamin B complex is yeast. When this product is concentrated under proper conditions, the various vitamins of the B complex are preserved. Large quantities of dried brewers' yeast may be given by adding it to soups, peanut butter, or catsup. In addition to yielding 16 mg. of thiamine, 1 mg. of riboflavin, and 11 mg. of niacin per 30 Gm. (1 ounce), dried brewers' yeast contains 14 Gm. of protein. Second in importance, as shown by Cook and Carroll,[397] are concentrates of rice polishings.

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394. Rynearson, E. H.: Journal-Lancet **62:** 4, 1942.
395. Spies, T. D., Bean, W. B., and Ashe, W. F.: J. A. M. A. **112:** 2414, 1939.
396. Unna, P. G.: Biochemie der Haut. Jena: Fischer, 1913.
397. Cook, C. A. and Carroll, R. H.: Indust. & Engin. Chem. **28:** 741, 1936.

Cutaneous Manifestations of Vitamin B Complex Deficiency

According to Ruffin,[398] Rosenblum and Jolliffe,[399] and other authorities, lesions of the mouth are the earliest manifestations of B complex deficiency. By far the most important finding is that of a smooth, atrophic tongue. The atrophy first appears at the tip and along the sides. The whole tongue may be slick and shiny. It is generally more red than normal and may have a beefy appearance. This marked redness may be present despite severe anemia. In addition to the changes in the tongue, crevices at the corners of the mouth are frequently observed, usually bilateral, varying from small cracks to deep fissures; the latter may bleed and are sometimes painful.

Martin and Koop[400] found that the abnormal changes in the oral mucosa resulting from avitaminosis B constitute a highly important etiologic factor in mouth cancer.

Gross[225] reported a series of extensive and localized cutaneous eruptions apparently beginning as so-called seborrheic dermatitis and associated with gastric hypo-acidity or anacidity. These skin lesions failed to yield to the usual dermatologic therapy but responded well to large parenteral doses of crude liver extract (Figs. 48, 49). Gross carefully points out, however, that this treatment is by no means always effective in seborrheic dermatitis. The explanation for this may be that seborrheic dermatitis is not a uniform entity.

As a demonstration of the interrelation between vitamin B complex deficiency and cutaneous infections, Gross[225] cites cases of extensive moniliasis of the skin in diabetics which yield to parenteral liver therapy without any local measures. He and Rudy and Hoffman[224] are of the opinion that skin diseases in diabetics are not attributable to hyperglycemia or glycosuria, but rather to the skin's heightened vulnerability resulting from a deficiency in the vitamin B complex (however, see p. 88).

Stryker and Halbeisen[401] called attention to a clinical syndrome consisting of dermatitis and macrocytic anemia resulting from vitamin B complex deficiency. The cutaneous lesions in the early stages consisted of evanescent, patchy or diffuse, superficial, pruritic, scaly, dry or vesicular erythroderma. In the later stages the patches lost their transitory character, became confluent, and the vesiculation tended to disappear. The lesions were usually distributed on the face, the sides of the neck (Fig. 50), the anterior part of the shoulders, the upper part of the chest, and the

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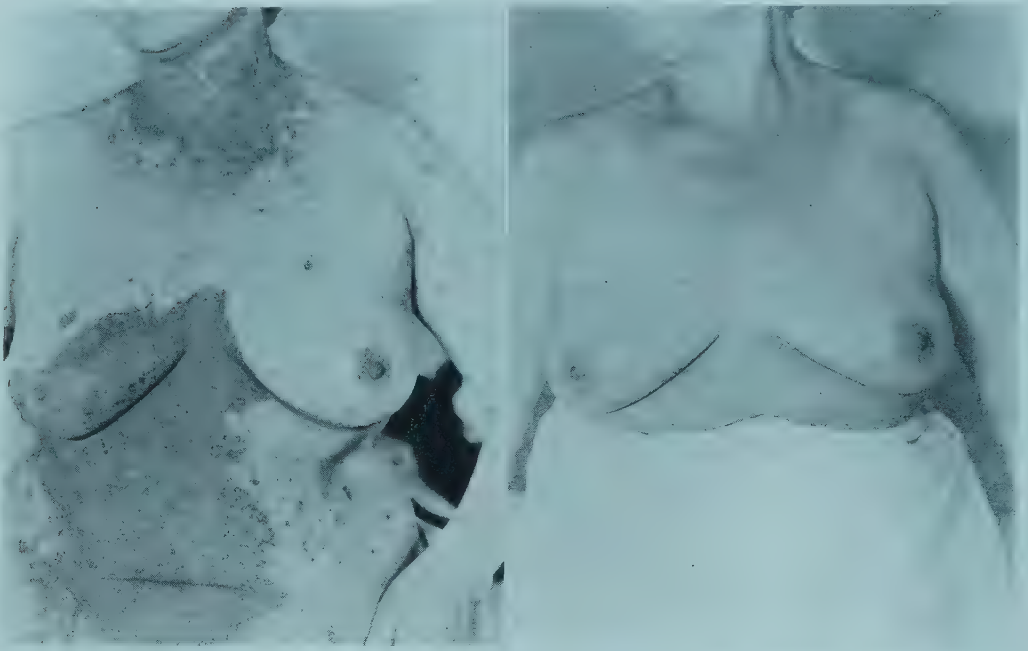
398. Ruffin, J. M.: J. A. M. A. 117: 1493, 1941.
399. Rosenblum, L. A. and Jolliffe, N.: J. A. M. A. 117: 2245, 1941.
400. Martin, H. and Koop, C. E.: Am. J. Surg. 57: 195, 1942.
401. Stryker, G. V. and Halbeisen, W. A.: Arch. Dermat. & Syph. 51: 116, 1945.



EFFECT OF CRUDE LIVER THERAPY ON SEBORRHEIC DERMATITIS

FIG. 48 FIG. 49

FIG. 48. Seborrheic Dermatitis of Several Years' Duration.
FIG. 49. Appearance of Eruption after Crude Liver Therapy.

(Courtesy of Dr. P. Gross and the Archives of Dermatology and Syphilology.)

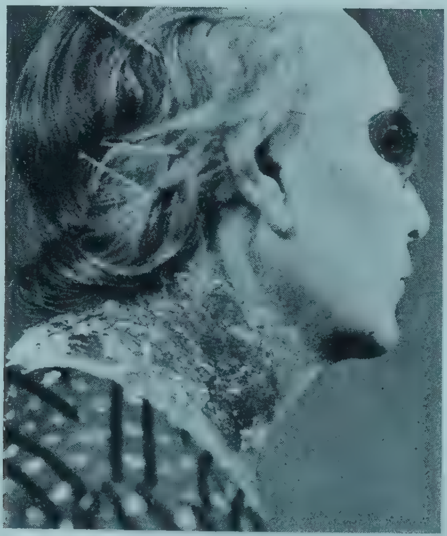


FIG. 50. DIFFUSE SQUAMOUS DERMATITIS OF THE NECK IN ASSOCIATION WITH MACROCYTIC ANEMIA DUE TO VITAMIN B COMPLEX DEFICIENCY

(Courtesy of Dr. G. V. Stryker and the Archives of Dermatology and Syphilology.)

areas immediately adjacent to the anterior axillary folds. Sometimes there were lesions of similar character on the extremities. All patients complained of intense itching. In addition, they exhibited mild mental depression, apprehension and fatigue. Study of the blood revealed a slight reduction of the erythrocytes, an increase in the mean corpuscular volume, and a decrease in the mean corpuscular hemoglobin concentration (method of Wintrobe[402]). Free hydrochloric acid was usually absent and the total acidity was low in the gastric secretion.

The response of the clinical symptoms, the improvement in the patient's general well-being, and the drop in the mean corpuscular volume as a result of parenteral injection of crude liver extract are very suggestive of a nutritional vitamin B deficiency similar to the cases described by Gross.[225]

The question may arise why the extensive eruptions due to B complex deficiency are not accompanied by other manifestations of niacin, riboflavin, or thiamine deficiency. While this cannot as yet be answered definitely, Gross[225] submits the following tentative explanations: (1) There may be predisposing factors in the integumental organ (e.g., a status seborrheicus) which permit a deficiency to become manifest in the skin, while other organs remain unaffected; (2) the cutaneous manifestations may be due to a deficiency of vitamin B complex factors other than riboflavin, niacin, or thiamine. The great obstacle to answering this question lies, of course, in the fact that we do not as yet possess any direct method of determining vitamin B complex deficiency in man. We may at present assume that a given case is due to a deficiency of the B complex as a whole only by noting that administration of the known B factors, either singly or in combination, is not curative while the whole complex produces therapeutic results.

Treatment consists of injections of large doses of crude liver extract (3 to 5 cc., twice or three times weekly) followed, after satisfactory clinical response, by weekly maintenance doses (1 to 2 cc.) continued for many months. For oral therapy, large doses of dried brewers' yeast or concentrates of rice polishings should be given in addition to a diet rich in vitamin B complex.

Allison[403] pointed out that the presence of hydrochloric acid in the stomach is essential for the absorption of vitamin B complex. He therefore recommends administration of hydrochloric acid whenever vitamin B complex therapy is indicated.

bb. Thiamine Deficiency

Vitamin B_1 or thiamine hydrochloride, the heat-labile fraction of the vitamin B complex, plays an essential role in the intermediate carbohydrate metabolism in all living cells. Thiamine is converted, in the body, to thiamine pyrophosphate (co-carboxylase), which functions as a co-enzyme in the decarboxylation of pyruvic acid to form acetaldehyde and carbon dioxide.

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[402] WINTROBE, M. M.: Am. J. M. Sc. 177: 513, 1929.

[403] ALLISON, J. R.: South. Med. J. 38: 235, 1945.

Deficiency in vitamin B_1 leads to beriberi, a disease characterized by symptoms due to damage to the peripheral nervous system and the cardiovascular system, thereby causing neuritis and heart failure.

No specific dermatologic condition has been ascribed to the lack of thiamine, although Elsom et al.[404] has reported that the skin may show pallor, flabbiness, and inelasticity which generally respond to treatment with vitamin B_1. However, Mashkilleison[405] reported that thiamine hydrochloride has a satisfactory influence on chronic dermatitides when administered in daily doses of 20 mg. over a period of three weeks. Special mention must be made, however, of the gratifying results obtained with vitamin B_1 in acrodynia (synonyms: pink disease, Swift-Feer disease). This is a rare condition occurring in infants and is characterized by cold, clammy, pink or dusky red hands and feet, and usually also by a generalized eruption of small red papules accompanied by excessive sweating (generalized or confined to the extremities), paresthesia, and photophobia. While no specific treatment for this disease is known, Durand et al.[406] found that intramuscular injections of 6 mg. of thiamine daily for six days and subsequently on alternate days brought this disorder under control. Good results with this treatment have also been reported by Forsyth,[407] Williams et al.,[408] and Groom.[409] However, oral administration of thiamine has proved to be ineffective in acrodynia.

The efficacy of large parenteral doses of thiamine in relieving pain in herpes zoster has been reported by Goodman[410] and confirmed by others, including the present writer. Alleviation of the pain in leprous neuritis was described by Badger and Patrick.[411] Ochsner and Smith[412] noted that this treatment effectively reduced the discomfort in varicose ulcers. Rattner and Roll,[413] on the other hand, found thiamine to be ineffectual in a considerable number of herpes zoster patients.

Of special interest to the dermatologist are the good results reported by Martin[414] and Imler[415] and their associates in treating irradiation sick-

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404. Elsom, K., Lewy, F. H., and Heublein, G. W.: Am. J. M. Sc. **200:** 757, 1940.
405. Mashkilleison, L. N., Benyamovich, E. B., Krichevskaya, E. D., and Shatamova, L. V.: Am. Rev Soviet Med. **3:** 19, 1945.
406. Durand, J. I., Spickard, V. W., and Burgess, E.: J. Ped. **14:** 74, 1939.
407. Forsyth, G.: M. J. Australia **2:** 751, 1939.
408. Williams, P., Shapiro, B. G., and Bartelot, R.: Lancet **1:** 76, 1940.
409. Groom, R. J.: Rocky Mountain M. J. **38:** 616, 1941.
410. Goodman, M. J.: California & West. Med. **51:** 105, 1939.
411. Badger, L. F. and Patrick, D. W.: Pub. Health Rep. **59:** 969, 1938.
412. Ochsner, A. and Smith, M. C.: J. A. M. A. **114:** 947, 1940.
413. Rattner, H. and Roll, H. C.: J. A. M. A. **112:** 2585, 1939.
414. Martin, C. L. and Moursund, W. H. Jr.: Radiology **30:** 277, 1938.
415. Imler, A. E. and Wammock, H.: Am. J. Roentgenol. **43:** 243, 1940.

ness with vitamin B_1 preparations, including concentrated rice polishings, or with injections of 10 mg. of thiamine hydrochloride. Wallace[416] succeeded in eliminating many of the symptoms of irradiation sickness, notably the severe nausea and vomiting, by administering thiamine hydrochloride parenterally concurrently with irradiation.

Lastly, it should be noted that certain skin manifestations (maculopruginous eruptions, local and generalized urticaria) occasionally make their appearance following repeated injections of thiamine. Of special interest is a report by Mitrani[417] of a patient who developed an eruption after the very first injection of thiamine. The author assumes that the organism had been sensitized by the natural thiamine contained in the food.

The principal sources of thiamine hydrochloride are lean pork, dried brewers' yeast, rice polishings, wheat germ, liver, heart, kidney, whole grain cereals, nuts, egg yolk, dried beans and peas, and skim milk. With the exception of pork, no single food contains enough thiamine to meet the organism's requirements. Moreover, the usual methods of cooking, involving significant loss of vitamins in the discarded cooking water, considerably reduce the amounts of vitamin actually ingested. Since the body is incapable of storing any appreciable amounts of thiamine, the daily intake must be adequate. Consequently the daily supply must be derived from a combination of foods. Acting in accordance with the recommendations of the Committee on Food and Nutrition of the National Research Council, the nation's millers and bakers have made available "enriched flour" and "enriched bread." The latter contains per pound a minimum of 1 mg. of thiamine hydrochloride, 4 mg. of nicotinic acid, and 4 mg. of iron. In this country millers and bakers in many states are required by law to add thiamine to white flour.

According to the current recommendation of the National Research Council, the daily optimum requirement of thiamine hydrochloride is 2.0 to 2.5 mg. for adults, depending on their activity. As for children, the optimum intake allows at least 0.03 mg. for each 100 calories. Patients receiving glucose intravenously require greater amounts of thiamine. Since large doses are promptly excreted through the kidneys, thiamine is more effective when given in several smaller doses of 10 mg. each.

Parenteral administration of vitamin B_1 is indicated when absorption from the gastrointestinal tract is impaired. Moreover, for dermatologic conditions only the parenteral route is of value, as discussed above.

cc. Riboflavin Deficiency

Riboflavin (synonymous terms: vitamin B_2, vitamin G, lactoflavin) plays an essential role in biologic oxidation by enabling the organism to synthesize Warburg's "yellow enzyme" from its constituent materials. Apparently riboflavin itself cannot be synthesized by animal cells and must therefore be supplied in the diet.

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[416] Wallace, W. S.: South. Med. J. 34: 170. 1941.

[417] Mitrani, M. M.: J. Allergy 15: 150, 1944.

The symptoms of riboflavin deficiency in man, first described by Sebrell and Butler,[418] may be divided into three groups: oral, cutaneous, and ocular.

The oral manifestations consist of stomatitis at the angles of the mouth, cheilosis, and glossitis. Possibly the earliest sign is pallor of the mucosa of the lips in the corners of the mouth, leading to a sodden condition of the mucocutaneous junction, with heaping up of the epithelium and cracking. This is followed by redness and desquamation, then by denudation of the mucosa, which may progress to the point of ulceration. In addition, fissures make their appearance at the angles of the mouth, leading to the formation of rhagades and, in severe cases, to permanent scarring. There is very little inflammatory reaction. This condition has been termed "angular stomatitis." It is to be noted, however, that fissuring at the corners of the mouth is not always due to a riboflavin deficiency. There is an entity known as perlèche, an intertrigo of the labial commissures, which may be mistaken for the angular stomatitis due to ariboflavinosis. The causes of perlèche and its differential diagnosis are discussed in some detail on page 463.

The lesions on the lips begin with abnormal redness of their buccal vermilion portion, which is covered at this stage with a thin grayish coat that subsequently desquamates, leaving the lips abnormally red along the line of closure. This condition is called "cheilosis." It is sometimes accompanied by shallow ulceration, crusting, and vertical fissures. However, cheilosis is not a characteristic manifestation of riboflavin deficiency alone. The condition has been observed to respond equally well to riboflavin, pyridoxine, and niacin, as well as to the entire vitamin B complex in the form of yeast and liver extract. The most likely explanation of this finding is that cheilosis is to be regarded as a manifestation, not of a single, but of a multiple deficiency (Gordon and Sevringhaus,[347] Ruffin and associates[419]). Moreover, as will be discussed in some detail in the section on cheilosis, changes in the lips may be due to other than nutritional causes.

The buccal mucous membranes may present grayness, thickening, and puckering, creating a picture resembling that of an early leukoplakia (Butler[420]).

The tongue is usually smooth, with the papillae flat or mushroom shaped, while the color is purplish red or magenta rather than the scarlet red characteristic of niacin deficiency. The chief complaint is pain, especially

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418. Sebrell, W. H. Jr. and Butler, R. E.: Pub. Health Rep. **53:** 2282, 1938; **54:** 2121, 1939.
419. Cayer, D., Ruffin, J. M., and Perlzweig, W. A.: South. Med. J. **38:** 111, 1945.
420. Butler, R. E.: M. Clin. North America **27:** 399, 1943.

when taking hot food; and this, together with a superficial glossitis, may be the earliest symptom of riboflavin deficiency (Purcell[421]). In the later stages, the oral lesions are accompanied by soreness and burning of the tongue and lips, making it distressing for the patient to open his mouth and sometimes even difficult for him to swallow, thus interfering with eating. In pellagra both forms of glossitis (riboflavin and niacin glossitis) are often present at the same time. In order to distinguish between the two, it may be necessary to make a clinical trial with riboflavin and then with niacin if the former fails.

Riboflavin deficiency may express itself in various types of *cutaneous manifestations*. There may be a fine, scaly slightly crusty desquamation on a mildly erythematous base, localized in the nasolabial folds, the alae nasi, the forehead, the malar eminences, as well as in the nostrils, and on or about the ears. Jolliffe and associates[422] have described facial lesions consisting of filiform excrescences from the sebaceous glands, varying in length up to 1 mm. and closely to sparsely scattered over the skin of the face. Their characteristic localization is in the nasolabial folds, but they are also commonly observed on the alae nasi, less commonly on the bridge of the nose, and occasionally on the forehead above the eyebrows. This dysfunction of the sebaceous glands, together with comedones, produces a picture which is sometimes called "sharkskin dermatitis" or "sharkskin appearance."

Butler[420] cautions against confusing the seborrheic accumulations described above with true seborrheic dermatitis. The absence of seborrheic involvement of the hairy areas of the body, notably the scalp, should suggest the possibility of riboflavin deficiency. In occasional cases, a severe dermatitis of the seborrheic type involves the whole face and neck (Sydenstricker[423]).

A fine scaly dermatitis of the hands, and areas of dermatitis around the anus, perineum, and vulva, have been observed to heal, simultaneously with remission of the mouth lesions, following the administration of riboflavin (Spies and Butt[424]). Nair[425] coined the term "orogenital syndrome" to designate a condition consisting of concurrent dermatitis of the scrotum and angular stomatitis due to riboflavin deficiency. The scrotal dermatitis has also been quite frequently observed by Purcell[421] and Mitra.[426]

Fissures may be seen at the commissure of the eyelids and at the nasal

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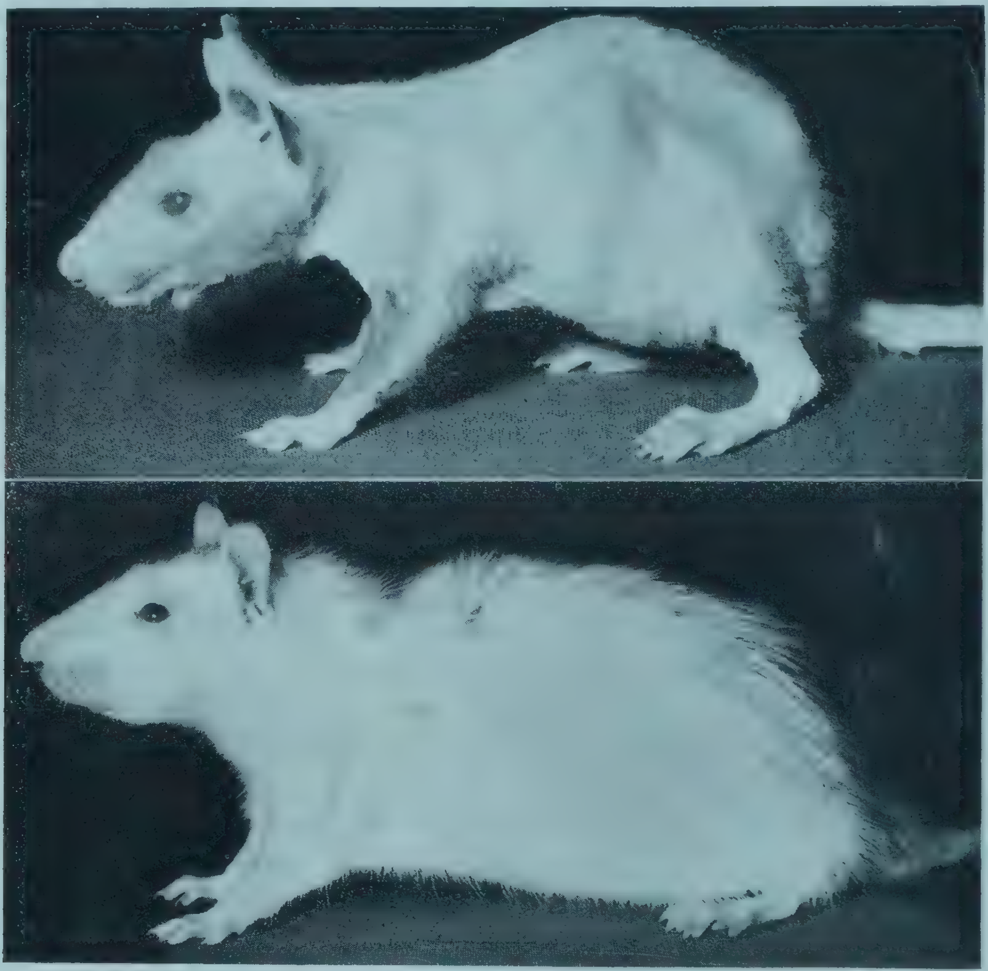
421. Purcell, F. M.: Tr. Roy. Soc. Trop. Med. & Hyg. **35:** 323, 1942.
422. Jolliffe, N., Fein, H. D., and Rosenblum, L. A.: New England J. Med. **221:** 921, 1939
423. Sydenstricker, V. P.: Ann. Int. Med. **14:** 1499, 1941.
424. Spies, T. D. and Butt, H. R.: Diseases of Metabolism, ed. by Duncan, G. G. Philadelphia: Saunders, 1942.
425. Nair, V. G.: J. Indian M. A. **8:** 215, 1939.
426. Mitra, K.: Indian Med. Gaz. **78:** 330, 1943.

orifices. The latter lesions may be accompanied by ulceration at the border of the external nares.

György,[427] Sullivan,[355] and their co-workers observed the following symptoms in rats kept on a diet deficient in riboflavin: mild, generalized scaling; partial alopecia; increased activity of the sebaceous glands during the early part of the diet, followed by disintegration of these glands in the later phases; and, in the final stage, atrophy of the epidermis, cutis, and cutaneous appendages. The foregoing signs responded promptly to administration of riboflavin (Fig. 51, 52).



Riboflavin Deficiency

Fig. 51 (upper). Riboflavin-deficient rat showing marked generalized dermatitis.
Fig. 52 (lower). Same animal after two months of treatment with riboflavin.

(Courtesy of Nutrition Department, The Upjohn Laboratories.)

The *ocular symptoms* consist of photophobia, burning and itching of the eyes, visual fatigue, and dimness of vision which is not relieved by the correction of refractive errors. The physical changes include circumcorneal injection which may be visible grossly or only on examination with the slit lamp. The next stage is an actual invasion of the cornea by small capillaries arising from the apices of the scleral loops. Superficial and even general vascularization of the cornea may follow.

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[427] György, P., Sullivan, M., and Karsner, H. T.: Proc. Soc. Exper. Biol. & Med. 37: 313, 1937.

Riboflavin has proven effective in the management of rosacea keratitis, but it is virtually useless in the skin manifestations of rosacea (Conners et al.[428]). However, according to Mashkilleison,[405] the simultaneous oral administration of riboflavin in large doses (50 mg. three times daily) plus niacin (100 mg. three times daily) frequently brings excellent therapeutic results in skin manifestations of rosacea.

The order in which the lesions of the mouth, skin, and eyes become evident may vary from one individual to another. Thus, in some cases the conjunctival and corneal lesions are the first to appear and are followed by those of the mouth and skin; in other cases the lesions at the angles of the mouth are the first signs of ariboflavinosis, and in still others the oral and ocular lesions are preceded by changes in the skin, particularly over the bridge of the nose, and in the folds of the alae nasi (Spies and Butt[424]).

Diagnosis of Riboflavin Deficiency: The patient should be examined for the characteristic signs and symptoms described above, namely, cheilosis, seborrheic-like dermatitis, glossitis, corneal vascularization, keratitis, photophobia, and conjunctivitis. The diet should be carefully investigated. Clinical observations may be supplemented by determination of the riboflavin excreted in the urine. In ariboflavinosis the urinary output of riboflavin is decreased usually to levels of between 800 to 1,200 micrograms. Generous doses of riboflavin should be administered and the clinical response closely observed.

Riboflavin is abundant in nature. Good sources are: dried yeast, lean beef or pork, milk, beef liver, kidney, heart, wheat germ, cheese, eggs peanuts, prunes, beet greens, turnip greens, dried beans, and peas. One serving of meat or liver plus one quart of milk supplies almost enough riboflavin to meet the adult human requirements for one day. It should be noted, however, that a considerable percentage of the riboflavin may be lost when meat is baked, roasted, or fried, and when milk is boiled under alkaline conditions.

Factors predisposing to deficiency are: (1) *Inadequate intake* due to poverty, improper food habits, or destruction of the vitamin by the use of alkalies in cooking vegetables. (2) *Inadequate absorption and assimilation* due to diarrhea, intestinal dysfunction, liver disease. (3) *Increased requirements* due to increased metabolic rate (e.g., increased physical activity), pregnancy, and lactation.

Recommended daily requirements: See page 148.

Therapy: Before treatment is begun, the cause of the deficiency should be determined and controlled. Therapy consists of putting the patient on an optimal balanced diet supplemented by 2 to 5 mg. of riboflavin by mouth three times a day. In the presence of gastric achlorhydria, a daily total of 15 mg. is required. In the event of impaired absorption due to vomiting or diarrhea and in hypothyroidism, riboflavin should be administered parenterally (10 to 50 mg. subcutaneously or intravenously).

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[428] Conners, C. A., Eckhardt, R. E., and Johnson, L. V.: Arch. Ophth. **29**: 956, 1943.

Lastly, it should be stressed that ariboflavinosis is rarely encountered as a single deficiency; it is most often associated with niacin deficiency. Therefore, if the clinical symptoms of ariboflavinosis fail to respond satisfactorily to specific therapy, crude liver extract and dried yeast should also be tried.

dd. Niacin Deficiency

Nicotinic acid, now officially termed "niacin," is another specific factor of the vitamin B complex. Niacinamide, the amide of nicotinic acid, is a constituent of two important enzymes, co-enzyme I (cozymase) and co-enzyme II. These substances play an important role in fermentation, carbohydrate metabolism, and tissue respiration and presumably act in a manner similar to that of riboflavin, taking on and giving off an atom of hydrogen. These compounds are, therefore, of vital importance in biologic oxidation. In cases of niacin deficiency, the cozymase content of the liver and muscle tissue is demonstrably subnormal. Factors predisposing to niacin deficiency are: (1) Inadequate intake due to poverty, ignorance, alcoholism, reducing regimens, or unbalanced therapeutic diets. (2) Inadequate absorption due to diarrhea or intestinal dysfunction. (3) Increased requirements due to high carbohydrate diet, violent exercise, increased metabolism.

In 1937, Elvehjem and associates[429] showed that niacin could cure "black tongue" in dogs, a disease long regarded as the counterpart of human pellagra. They also demonstrated that canine "black tongue" is indeed caused by niacin deficiency. Fifteen years earlier, Goldberger and his co-workers[430, 431] had established the fundamental fact that pellagra is a deficiency disease by demonstrating the efficacy of liver in curing the skin lesions. However, the exact nature of Goldberger's pellagra-preventive (P-P) factor in liver extract and yeast remained unknown until 1937, when Fouts et al.[432] and, shortly thereafter, Spies and co-workers[433] found niacin to be the chief P-P factor. We now know that pellagra is to be

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429. Elvehjem, C. A., Madden, R. J., Strong, F. M., and Wooley, D. W.: J. Am. Chem. Soc. **59:** 1767, 1937; J. Biol. Chem. **123:** 137, 1938.

430. Goldberger, J. and Tanner, W. F.: J. A. M. A. **79:** 2132, 1922.

431. Goldberger, J., Wheeler, G. A. and Tanner, W. F.: Pub. Health Rep. **40:** 927, 1925.

432. Fouts, P. J., Helmer, O. M., Lepkowsky, S., and Jukes, T. H.: Proc. Soc. Exper. Biol. & Med. **37:** 405, 1937.

433. Spies, T. D., Cooper, C., and Blankenhorn, M. A.: J. A. M. A. **110:** 622, 1938.

regarded as a multiple deficiency disease. Niacin is specific for the treatment of the alimentary and dermal lesions, as well as of the mental symptoms and the porphyrinuria exhibited by pellagrins. The polyneuritic manifestations, however, can be controlled only by thiamine hydrochloride: and the cheilosis so commonly seen in pellagrous patients responds only to riboflavin. It may be pertinent to recall here that the three mentioned vitamins are all members of the B complex and are generally present in the same foods. An inadequate supply of these foods is likely to result in at least some degree of multiple deficiency. For further information, the reader is referred to Sydenstricker's detailed discussion of the subject.[434]

Pellagra has been described as a disease of the three D's: dermatitis, diarrhea, and dementia. Since the skin lesions are dealt with rather extensively in Part Four, we shall consider only the other manifestations here.

Symptoms arising from involvement of the alimentary tract are, at first, not characteristic, consisting of anorexia, abdominal pain, and burning of the tongue. These gradually progress to intense glossitis, stomatitis, gingivitis, pharyngitis, gastritis, and enteritis. The lips may assume an erythematous and cracked appearance, while the tongue becomes fiery red, swollen, and smooth, except where it is indented by pressure of the teeth. The gums and the pharynx become red and ulcerated. Gastroscopic studies have revealed fiery red ulcerated lesions of the mucous membrane, closely resembling the mouth lesions (Spies et al.[435]). Achylia is noted in about 60 per cent of the cases. In advanced cases severe, persistent, watery diarrhea, severe abdominal pain, and distention are not uncommon.

The mucous membranes of the urogenital tract are often affected. Secondary infections are common, giving rise to severe vaginitis, urethritis, and endocervicitis. Vincent's organisms are found in abundance wherever the mucous membranes are involved by this disease.

Mental symptoms are commonly observed in pellagra. They begin with vertigo, confusion, mental depression, then progress to psychotic states, often of the paranoid type, characterized by hallucinations, delusions of persecution, and depression. Delirium may occur, and patients may become maniacal.

Pellagra is endemic in certain sections of the Southern states in this country, as well as on other continents, occurring chiefly among the poorer classes whose diet consists largely of the three staple food items: corn meal, salt pork, and molasses. The importance of this disease can be seen in the death rate. In 1928, the death rate from pellagra was 22.4

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434. Sydenstricker, V. P.: Arch. Int. Med. 67: 746, 1941.
435. Spies, T. D., Vilter, R. W., and Ashe, W. F.: J. A. M. A. 113: 931, 1939.

per 100,000 in our Southern states. However, the rate declined to 5.1 in 1940, owing to the rise in the standard of living and a favorable change in the food habits of the population (Remington[436]). Pellagra is also commonly encountered in alcoholics. This suggests that pathologic changes in the liver as well as dietary deficiency may be an etiologic factor in alcoholic pellagra.

Porphyrin is often excreted in the urine of patients with endemic or alcoholic pellagra, but porphyrinuria is not regarded as an essential feature of this disease (Kark and Meiklejohn[437]). Dobriner and associates[438] have suggested that some hepatic dysfunction may be the cause of the porphyrinuria so commonly seen in pellagra patients. Frontali[438a] found that in children with experimentally produced pellagra the porphyrin concentration in the blood was 10.5 micromilligrams per cent as against 6.5 micromilligrams in normal children. When the pellagrous children were treated with niacin the porphyrin level in the blood dropped to 6 micromilligrams per cent. Moreover, the rather marked porphyrin excretion in the urine of these children decreased to mere traces when they were on a mixed diet. More recently, however, doubt has been expressed as to whether the pigment in the urine really is porphyrin. According to Gordon and Sevringhaus[347] the pigment may be a urorosein or some other indole derivative.

It is well to bear in mind that pellagra cases need not necessarily present all the classic symptoms of the three D's. Mild cases showing only one or two of the signs are frequently encountered.

The effective therapeutic oral dose for the average pellagra patient is 500 mg. of niacinamide in ten doses of 50 mg. each given at hourly intervals. In severe cases a total daily dose of 1,000 mg. may be required to cure the skin and mucous membrane lesions and to relieve wholly or in part the gastrointestinal and mental manifestations. As mentioned above, the intravenous route (20 mg. two or more times daily) must be resorted to when absorption from the gastrointestinal tract is appreciably impaired. In addition, the patient should be given the other members of the B complex and a generous, well balanced diet (see p. 475).

According to Mashkilleison,[405] besides its antipellagra action, niacin has also a definite antipruritic effect, paticularly in certain cases of pruritus, lichen urticatus, and lichen ruber planus.

Of the many skin conditions in which niacin has been tried therapeutically, only a few have shown a promising response. Thus, Gilman[439] recommended niacin for the treatment of light hypersensitiveness; Stokes,[440]

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436. Remington, R. E.: South. Med. J. **37:** 605, 1944.
437. Kark, R. and Meiklejohn, A. P.: Am. J. Med. Sci. **201:** 380, 1941.
438. Dobriner, K., Strain, W. H., and Localio, S. A.: Proc. Soc. Exper. Biol. & Med. **38:** 748, 1938.
438a. Frontali, G.: Schweiz. med. Wchnschr. **72:** 208, 1942.
439. Gilman, R. L.: discussion to Anderson, N. P.: Arch. Dermat. & Syph. **37:** 822, 1938.
440. Stokes, J. H.: A Handbook of Fundamental Medical Dermatology. Philadelphia: Department of Dermatology Book Fund, University of Pennsylvania, 1942.

as well as the present writer, has observed gratifying results in some cases obtained with 100 mg. niacin three times a day. Kuehnau,[441] Stokes,[440] and Ebert[442] have seen cases of acute and subacute disseminated lupus erythematosus improve with oral doses (100 mg. three times a day) or with parenteral injections of 50 mg. of niacin three times a week. Ebert[442] reports, however, that a number of his cases failed to respond to niacin therapy. On the basis of our own observations we feel that niacin tends to counteract light hypersensitiveness in lupus erythematosus, without having any effect whatsoever on the underlying causes of this disease.

Miscellaneous conditions benefited by niacin therapy include certain types of leukoplakia oris, kraurosis vulvae, and psoriasis (see p. 475).

Several authors have recommended niacin therapy for toxic symptoms due to drugs. We personally have seen satisfactory results from daily doses of 100 mg. of niacinamide by mouth, three times a day.

Since Vincent's organisms are abundant in pellagra wherever mucous membranes are involved, King[443] has suggested that infections by these organisms may be related to niacin deficiency. King,[443] Schwartzman and Grossman,[444] and Johnson[445] have reported that niacin (25 to 50 mg. three times a day) is the most effective therapeutic agent in Vincent's ulceromembranous gingivostomatitis.

Spies and co-workers[446] found niacin to be effective in relieving nausea, vomiting, anorexia, and headache associated with x-ray therapy (see also thiamine, p. 170).

Niacin often causes flushing and erythema of the skin, owing to increased peripheral circulation and capillary dilatation, and should, therefore, not be given to patients with a tendency toward rosacea. Nicotinamide does not evoke this reaction and is equally effective in similar doses.

Niacin is abundantly present in yeast. Other good sources of this vitamin are liver, lean meats, canned salmon, poultry, and peanuts.

The daily requirements of niacin are listed in Table 45, p. 148.

ee. Pyridoxine Deficiency

Goldberger and Lillie[447] were the first to reproduce the characteristic manifestations of pyridoxine (vitamin B_6) deficiency in rats. Because of the peculiar distribution of the lesions, these authors thought this condition to be the counterpart of human pellagra and therefore termed it "rat pellagra." However, Goldberger's concept was disputed by Birch, György, and Harris[448] on the ground that niacin, the specific vitamin for both human pellagra and canine black tongue, is ineffective in "rat pellagra," which, on the other hand, can be cured by a diet containing foods that have no therapeutic value in human pellagra. These investigators suggested the term "rat acrodynia" because of its most conspicuous feature. They stressed the point that their choice of this term is entirely without prejudice as to whether or not the underlying disease is identical with acrodynia in human beings.

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[441] Kuehnau, W.: Klin. Wchnschr. **18:** 1117, 1939.

[442] Ebert, M. H.: M. Clin. North America **26:** 47, 1942.

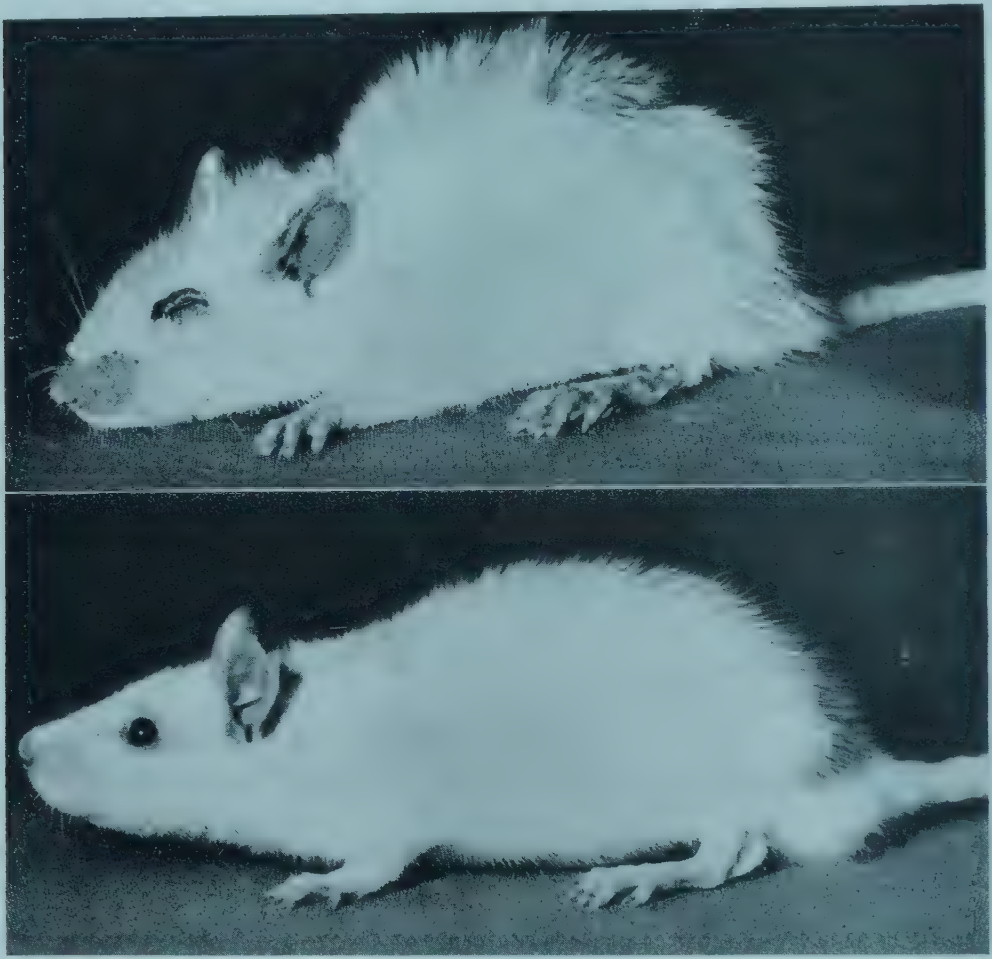
[443] King, J. D.: Lancet **2:** 32, 1940.

[444] Schwartzman, J. and Grossman, L.: Arch. Ped. **58:** 515, 1941.

[445] Johnson, W. M.: North Carolina M. J. **4:** 51, 1943.

[446] Spies, T. D., Bean, W. B., and Stone, R. E.: J. A. M. A. **111:** 584, 1938.

[447] Goldberger, J. and Lillie, R. D.: Pub. Health Rep. **41:** 1025, 1926.



PYRIDOXINE (VITAMIN B_6) DEFICIENCY

FIG. 53. Pyridoxine-deficient rat showing skin lesions limited to the paws, ears, and snout.

FIG. 54. Complete recovery following three weeks of treatment with pyridoxine hydrochloride.

(Courtesy of Nutrition Department, The Upjohn Laboratories.)

According to György,[449] Gross,[450] and Sullivan and Nicholls,[353] rat acrodynia is the expression not of one, but of two, deficiencies: (1) pyridoxine deficiency, which causes (a) thickening and crusting of the ears, (b) scaling, crusting, and swelling of the paws and the legs, (c) severe crusting of the tail, with ulceration and necrosis at the root, (d) frequent formation of abscesses in and adjacent to the area of the specific dermatitis (Figs. 53, 54); and (2) pantothenic acid deficiency, which causes (a) severe crusting of the nose and lips, (b) spectacled eye condition, (c) mild brown scaling of the tail, and (d) alopecia, especially of the face, head, and neck.

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[448] BIRCH, T. W., GYÖRGY, P., and HARRIS, L. J.: Biochem. J. 29: 2830, 1935.
[449] GYÖRGY, P.: Arch. Dermat. & Syph. 43: 230, 1941.
[450] GROSS, P.: J. Invest. Dermat. 3: 505, 1940.

Pyridoxine seems to play some part in the utilization of unsaturated fatty acids, at least in rats. As mentioned on page 92, Burr and Burr[17] demonstrated that rats placed on a diet lacking certain essential fatty acids will exhibit characteristic cutaneous manifestations. Some years later, Birch[451] and Quackenbush et al.[452] claimed that the fat-deficiency disease described by the Burrs was identical with so-called rat acrodynia caused by deficiency in pyridoxine and also in an accessory skin factor of the filtrate fraction, subsequently identified as pantothenic acid. Schneider et al.[453] and Salmon[454] demonstrated that rat acrodynia could be cured independently by essential fatty acids, on the one hand, and by pyridoxine plus the accessory factor, presumably pantothenic acid, on the other. Lastly, Gross[450] demonstrated a very interesting relationship between the two factors. He showed that therapeutic doses of oils rich in essential fatty acids do not prevent the appearance of the cutaneous manifestations of pyridoxine or of pantothenic acid deficiency but that, on the other hand, administration of pyridoxine is beneficial in rat acrodynia only when the animal is maintained on curative doses of essential fatty acids. Gross observed, moreover, that animals given pyridoxine and essential fatty acids are fully protected against pyridoxine deficiency, but nevertheless develop the skin lesions characteristic of pantothenic acid deficiency, and die from the lack of this factor. In brief, there definitely seems to be some correlation between pyridoxine and certain unsaturated fatty acids, at least in so far as the well-being of rats is concerned.

Well defined symptoms of pyridoxine deficiency have not been described in man. However, therapeutic doses of pyridoxine have proven beneficial in some cases of cheilosis which were refractory to riboflavin (Smith and Martin,[455] Machella[456]). Furthermore, Spies and co-workers[395] have shown that vitamin B_6 deficiency may accompany deficiency of other components of the vitamin B complex. These authors reported pellagrins who failed to respond to a selected diet supplemented with therapeutic doses of

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451. Birch, T. W.: J. Biol. Chem. **124:** 775, 1938.
452. Quackenbush, F. W., Platz, B. R., and Steenbock, H.: J. Nutrition **17:** 115, 1939.
453. Schneider, H., Steenbock, H., and Platz, B. R.: J. Biol. Chem. **132:** 539, 1940.
454. Salmon, W. D.: J. Biol. Chem. **133:** lxxxiii (Proceedings), 1940.
455. Smith, S. G. and Martin, D. W.: Proc. Soc. Exper. Biol. & Med. **43:** 660, 1940.
456. Machella, T. E.: Am. J. M. Sc. **203:** 114, 1942.

thiamine, riboflavin, and niacin, but who recovered after appropriate doses of vitamin B_6 had been added. Pyridoxine was found to be equally effective in a case of pellagra reported by Wright et al.[457]

György[449] has stressed the analogy between seborrheic cutaneous lesions in man and the manifestations caused by deficiency in pyridoxine and related factors in rats. According to Gross,[225] many patients with a seborrhea-like dermatitis show definite, although incomplete, improvement after liver therapy. Wright et al.[457] reported that pyridoxine injected in 25 to 100 mg. doses achieved definite improvement and, in some instances, complete disappearance of seborrheic eruptions in cases where all other measures had failed. Wright[458] has also observed gratifying responses to weekly subcutaneous injection of 50 mg. of pyridoxine in cases of non-seborrheic dermatitis in both adults and children. Lastly, Jolliffe and associates[459] had some success in treating persistent postadolescent acne vulgaris with 50 to 250 mg. of pyridoxine, daily in divided doses, by mouth. In many cases a marked reduction in the oiliness of the skin was noted, quite aside from the effect on acne. These authors suggest that pyridoxine may exert a corrective action on a deranged fatty acid or lipid metabolism of the skin.

Diagnosis of Pyridoxine Deficiency: Since no definite pyridoxine deficiency syndrome has been recognized in man, it is impossible to arrive at a diagnosis on the basis of clinical symptoms. However, evidence of inadequacy of other components of the B complex suggests the likelihood of a lack of pyridoxine as well. This particular deficiency is perhaps best determined by observing a favorable clinical response to a therapeutic test with liberal doses of pyridoxine hydrochloride. Pyridoxine may be given orally 50 to 250 mg. in divided doses, or 50 to 100 intravenously. Pain occurs when pyridoxine is injected intramuscularly.

Good sources of pyridoxine are dried yeast, liver, rice polishings, meat, fish, legumes, corn, and whole wheat. The potency of vitamin B_6 is expressed in terms of weight of the pure substance. The human requirement is not definitely known, but it is estimated to be about 2 mg. per day.

ff. Pantothenic Acid Deficiency

Pantothenic acid is one of the constituents of what has been called the "filtrate factor." The latter was formerly believed to consist of a single vitamin, and some investigtors have used the terms "pantothenic acid" and "filtrate factor" interchangeably. However, the weight of available evidence indicates that pantothenic acid is only one of several vitamins contained in the filtrate factor (Table 48, p. 165). Pantothenic acid is

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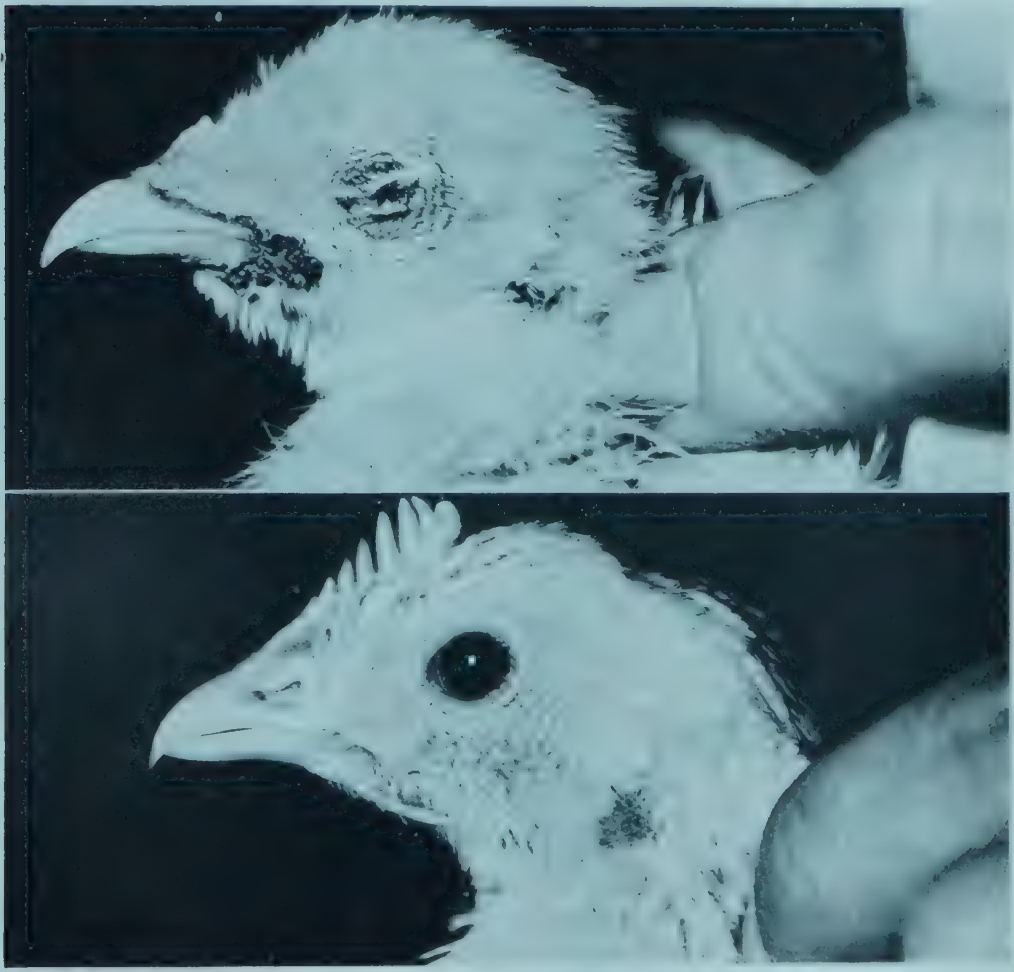
457. Wright, C. S., Samitz, M. H., and Brown, H.: Arch. Dermat. & Syph. **47:** 651, 1943.
458. Wright, C. S.: J. Michigan M. Soc. **41:** 744, 1942.
459. Jolliffe, N., Rosenblum, L. A., and Sawhill, J.: J. Invest. Dermat. **5:** 143, 1942.

usually prepared and used in the form of its calcium salt, calcium pantothenate.

In the preceding section it was pointed out that certain skin manifestations of rat acrodynia respond, not to pyridoxine, but to pantothenic acid. To avoid needless repetition, the reader is referred to page 181.



PANTOTHENIC ACID DEFICIENCY

FIG. 55. (Upper) Dermatitis in a chick produced by a diet deficient in pantothenic acid. The eyelids, corners of the mouth, and adjacent skin areas are involved. Feathering is retarded and rough.

FIG. 56. (Lower) Skin lesions completely cured within three weeks after calcium pantothenate was added to the diet.

(Courtesy of Nutrition Department, The Upjohn Laboratories.)

It has been shown that pantothenic acid serves to prevent and cure dermatitis in chicks—the so-called "chick pellagra" (Figs. 55, 56) – and to prevent or repair renal hemorrhage, atrophy, and necrosis in rats kept on a diet deficient in pantothenic acid (Woolley et al.,[460] Jukes[461]).

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460. WOOLLEY, D. W., WAISMAN, H. A., and ELVEHJEM, C. A.: J. Am. Chem. Soc. **61:** 977, 1939.

461. JUKES, T. H.: J. Am. Chem. Soc. **61:** 975, 1939.

Special interest has been evoked by the observation that the coats of rats, silver foxes, and dogs turn prematurely gray when the animals are kept on a diet deficient in pantothenic acid and that administration of pantothenic acid can correct (Fig. 57) the nutritional achromotrichia (Bakke et al.,[462] Morgan et al.,[463, 464] György and Poling,[465] Unna et al.,[466] Frost and Dann[467]). In view of the great significance attributed to these findings, we shall present the following summary of reports by Sullivan and Nicholls:[357] When young piebald rats were fed a purified diet low in the vitamin B complex and supplemented with synthetic forms of thiamine, riboflavin, pyridoxine, and niacin, growth was retarded and cutaneous alterations were observed. These consisted of changes in the luster and texture of the fur; mild general scaling; small dermatitic crusted plaques; diffuse alopecia of the abdominal and the preauricular regions; mild, diffuse scaling of the paws; scaling, ridging, and curling of the tail; and symmetric pattern graying of the fur of the hood. Histologically, there was mild hyperkeratosis and a slight amount of edema and vesiculation. There was a characteristic dilatation of the hair follicles. Supplementation with

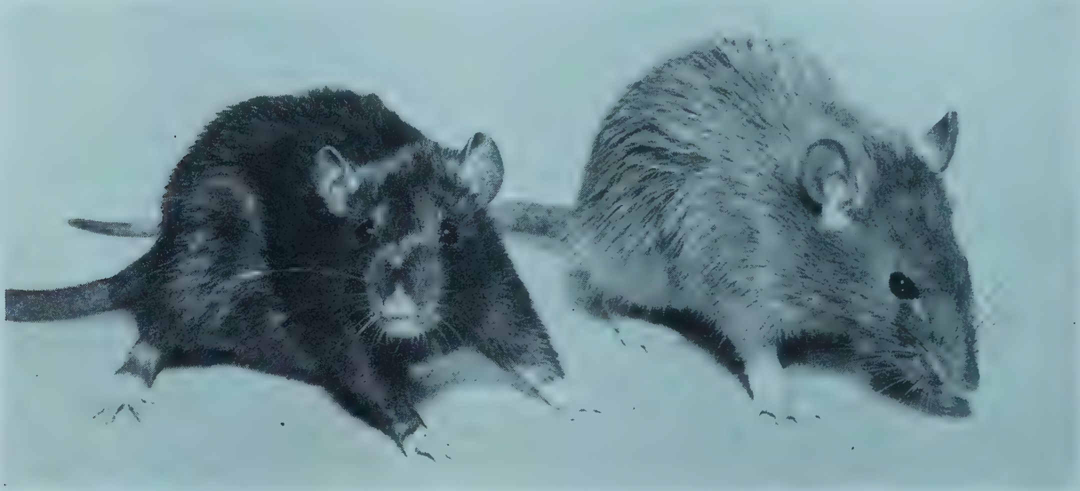

FIG. 57. NUTRITIONAL ACHROMOTRICHIA DUE TO PANTOTHENIC ACID DEFICIENCY

Litter mates at age of 90 days. Since 21 days of age, both animals received a diet free of vitamin B complex but with daily supplements of thiamine, riboflavin, and pyridoxine. One was given, in addition, a daily supplement of 100 micrograms of pantothenic acid, which the second rat did not receive, and developed practically complete achromotrichia.

(Courtesy of Research Laboratories, S. M. A. Corporation.)

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462. BAKKE, A., ASCHEHOUG, V., and ZBINDEN, C.: Compt. rend. Acad. de sc. **191:** 1157, 1930.
463. MORGAN, A. F., COOK, B. B., and DAVISON, H. G.: J. Nutrition **15:** 27, 1938.
464. MORGAN, A. F. and SIMMS, H. D.: J. Nutrition **20:** 627, 1940.
465. GYÖRGY, P. and POLING, C. E.: Proc. Soc. Exper. Biol. & Med. **45:** 773, 1940.
466. UNNA, K., RICHARDS, G. V. and SAMPSON, W. L.: J. Nutrition **22:** 553, 1941.
467. FROST, D. V. and DANN, F. P.: J. Nutrition **27:** 355, 1944.

pantothenic acid promoted growth and prevented and cured the generalized dermatitis and symmetric pattern grayness.

The morphologic explanation of the graying of the fur of rats on pantothenic acid deficiency diets was given by Ralli and Graef,[468] who demonstrated that the sudden graying is the result of atrophy of the hair bulbs and follicles, due to cessation of melanin deposition in tissues. It is also interesting to note Ralli's observation[468, 469] that graying of the fur occurs much earlier in animals on a low salt intake than in those on a high salt intake; and that adrenalectomy will bring about an increase in the deposition of melanin in the hair bulbs of rats graying as a result of pantothenic acid deficiency.

However, experiments in man have been uniformly negative (Blanderaone et al.[470] Vorhaus et al.,[471] Kerlan and Herwick,[472] Wright[458]). This shows, once again, that it is a mistake to assume that the findings in animal experiments must apply to conditions in man. The discrepancy in this particular case may be due to the fact that only young animals were used for these "graying" experiments, while in man the pantothenic acid is designed for use in adults whose hair is turning gray.

Pantothenic acid deficiency also seems to induce alopecia in mice; and it has been observed that administration of this vitamin promotes the growth of hair (Woolley[473]).

Good sources for pantothenic acid are dried yeast, liver, rice polishings, whole grain cereals, egg yolk, and other foods rich in the B complex. The potency is expressed in terms of weight of pure calcium pantothenate.

The daily requirement has been estimated to be approximately 5 to 10 mg. daily. For therapy, doses of 10 to 50 mg. have been suggested.

gg. Para-Aminobenzoic Acid Deficiency

Para-aminobenzoic acid, another member of the B complex group, has been shown by Ansbacher[474] to be an achromotrichia factor in rats. He produced graying of the fur of rats on a synthetic ration, which could be cured by the administration of para-aminobenzoic acid. This achromotrichia was not related to pantothenic acid, since the ration contained an adequate amount of this vitamin. This would seem to demonstrate that the B complex contains several different anti-gray hair factors.

However, despite the allegations of early investigators in this field, there is no clinical evidence that, in man, pantothenic acid can either

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468. Ralli, E. P. and Graef, I.: Endocrinology **32:** 1, 1943.
469. Ralli, E. P., Clarke, D. H., and Kennedy, E.: J. Biol. Chem. **141:** 105, 1941.
470. Brandaleone, H., Main, E., and Steele, J. M.: Proc. Soc. Exper. Biol. & Med. **53:** 47, 1943.
471. Vorhaus, M. G., Gompertz, M. L. and Feder, A.: Am. J. Digest. Dis. **10:** 45, 1943.
472. Kerlan, I. and Herwick, R. P.: J. A. M. A. **123:** 391, 1943.
473. Woolley, D. W.: Proc. Soc. Exper. Biol. & Med. **46:** 565, 1941.
474. Ansbacher, S.: Science **93:** 164, 1941.

convert the gray color of the hair to black (Eller and Diaz,[475] own experiments), or restore pigmentation in vitiligo, or induce depigmentation of lentigines (Beinhauer[476]). Moreover, it is rather difficult to accept the idea that a condition so universal as gray hair could be a sign of nutritional deficiency disease due to dietary inadequacy.

hh. Inositol Deficiency

According to Woolley,[477] inositol is the anti-alopecia factor in mice. When young mice are kept on a diet completely lacking in inositol, their growth is soon interrupted and they become completely bald over large areas of the body. The alopecia can be cured by addition of inositol to the fodder. The addition of pantothenic acid, the absence of which may also give rise to hair changes, proved useless in these animals, and supplementation with para-aminobenzoic acid or with biotin did not achieve any results whatsoever.

Vorhaus et al.[471] failed to obtain any curative results with 1 to 2 Gm. daily of inositol in patients with alopecia. However, these authors observed in two of their cases that generalized pruritic eruptions definitely subsided under therapy with this vitamin. In addition, inositol appears to be an essential factor in fat metabolism. Thus, it has been observed to have a curative effect on biotin-induced fatty livers in rats (Gavin and McHenry[478]).

Good sources of inositol are muscle tissue, liver, rice polishings, wheat germ, cereals, and soy bean phospholipids.

ii. Biotin Deficiency

Biotin, also known as vitamin H or co-enzyme R, is said to be biologically the most potent member of the vitamin B complex, and physiologically one of the most active chemical substances known, as measured by yeast growth. In mammals, biotin deficiency develops only when raw egg white is added to a diet inadequate in biotin. This is due to the fact that biotin combines chemically with a substance called "avidin" (because of its avidity for biotin), considerable quantities of which are present in uncooked egg white (György et al.[21]). As a result of this chemical union, biotin cannot be absorbed in the intestinal tract and is excreted in the feces. Both experimental animals and man present a characteristic syndrome, known as "egg white injury," in response to induced biotin deficiency. Avidin, which has been isolated in pure form from white of eggs, produces this condition only when given orally and when the diet is deficient in

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475. Eller, J. J. and Diaz, L. A.: New York State J. Med. **43:** 1331, 1943.
476. Beinhauer, L. G.: Arch. Dermat. & Syph. **49:** 132, 1944.
477. Woolley, D. W.: J. Biol. Chem. **139:** 29, 1941.
478. Gavin, G. and McHenry, E. W.: J. Biol. Chem. **139:** 485, 1941

biotin. The combination of avidin with biotin is readily disrupted by heat.

As early as 1933, Parsons et al.[479] produced a characteristic pathologic condition in rats with a diet containing large amounts of raw egg white and successfully repeated the experiment some years later in rabbits and monkeys.[480] Parsons concluded that the damage was due to the combined action of a positive toxicity and a relative absence of a protective factor. Shortly thereafter, György named this factor "vitamin H" (*H* for *Haut*, the German word for "skin"). Lastly, du Vigneaud, György, et al.[481] established the identity of biotin and vitamin H.

A characteristic dermatoses makes its appearance in young rats kept on a diet in which the source of protein consists essentially of unheated and uncoagulated commercial dried egg white. The initial symptoms consist of a dermatitis which is at first confined to the groins, genitalia, the neck, and the area around the mouth. As György[449] points out, this is almost completely analogous to intertrigo in infants, which is commonly one of the first manifestations of seborrheic dermatitis. After this initial phase brown, adherent scales of varying size and thickness make their appearance, being generally confined to the back. György stresses the similarity between these lesions and the "cradle cap" of seborrheic dermatitis in infants. The pigmentation of the scales is a result of their high fat (cholesterol) content. In later stages, there is a generalized erythematous, scaly, greasy, pruritic dermatitis which, according to György, resembles the exfoliative seborrheic dermatitis seen in adults or its counterpart in infants, erythroderma desquamativum (Leiner's disease). The dermatitis involving the eyelids of the animals creates a picture commonly known as "spectacled eyes." The epidermis of the rat is shed in thin scales, large and small, which, because of their rapid and continuous production, become devoid of fat and therefore colorless. Generalized alopecia often occurs (Fig. 58) In black and piebald rats the coat shows signs of depigmentation, the hair turning brownish or even gray. Mild, sublingual ulcers are fairly common. Spastic gait, probably due to hypertonicity of the striated muscles, particularly of the hind legs, is a characteristic symptom of egg white injury in the advanced stage. Microscopic examination reveals extensive hyperkeratosis, some parakeratosis, acanthosis, and edema. There is an excessive amount of sudanophilic fat in the hyperkeratotic lamellae (Sullivan and Nicholls[356]). Administration of biotin results in restoration of the integrity of the skin, as judged by gross and microscopic inspection.

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479. Parsons, H. T., Lease, J. G., and Kelly, E.: J. Biol. Chem. **100:** 77, 1933.
480. Lease, J. G., Parsons, H. T., and Kelly, E.: Biochem. J. **31:** 433, 1937.
481. du Vigneaud, V., Melville, D. B., György, P., and Rose, C. S.: Science **92:** 62, 1940.

Hegsted et al.[482] found typical dermatitis involving the feet to be characteristic of biotin deficiency in chicks; and Patrick and associates[483] have noted a similar dermatitis in turkeys due to the same cause.

With the cooperation of four volunteers who adhered to an experimental diet extremely poor in biotin and containing desiccated egg white in amounts sufficient to provide about 30 percent of the total caloric intake, Sydenstricker and his collaborators[484] succeeded in producing the biotin deficiency syndrome in man. This diet was supplemented with various vitamins as well as with iron and calcium. The egg white injury which developed within four weeks was characterized by a desquamating dermatitis. During the seventh week increasing dryness and scaliness were observed, together with a grayish pallor of the skin and mucous membranes, which was out of proportion to the blood picture. Other symptoms noted were atrophy of the papillae of the tongue, which remained pale, in contrast to the congested tongue seen in pellagra and in ariboflavinosis; and various nervous disturbances (depression, somnolence, paresthesias). The urinary excretion of biotin was from 3.5 to 7.3 micrograms in twenty-four hours, as compared with 29 to 62 micrograms in individuals on a

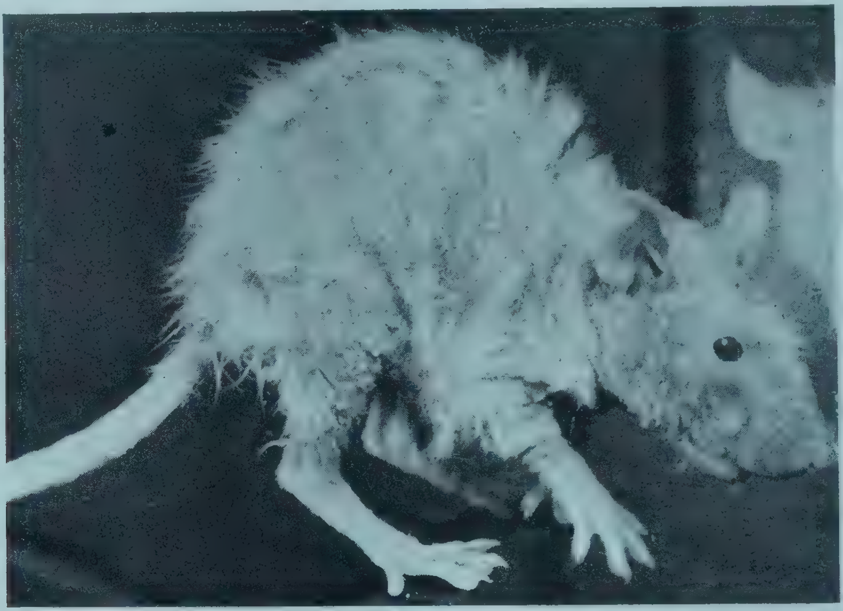

FIG. 58. BIOTIN DEFICIENCY

Severe seborrheic dermatitis-like skin eruption in a rat on a biotin-deficient diet (Courtesy of Parke, Davis and Company.)

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482. HEGSTED, D. M., OLESON, J. J., MILLS, R. C., ELVEHJEM, C. A., and HART, E. B.: J. Nutrition **20:** 599, 1940.

483. PATRICK, H., BOUCHER, R. V., DUTCHER, R. A., and KNANDEL, H. C.: Proc. Soc. Exper. Biol. & Med. **48:** 456, 1941.

484. SYDENSTRICKER, V. P., SINGAL, S. A., BRIGGS, A. F., DE VAUGHN, N. M., and ISBELL, H.: J. A. M. A. **118:** 1199, 1942.

normal diet. The abiotinosis was promptly corrected by parenteral administration of biotin concentrate (75 to 300 micrograms daily).

Williams[485] has reported the occurrence of the clinical biotin deficiency in a patient who, during the six years preceding his hospitalization, had partaken of a diet consisting almost exclusively of from 2 to 6 dozen raw eggs a week, accompanied by from 1 to 4 quarts of wine daily. Large areas of the patient's skin were red and scaling. Biopsy showed microscopic changes in the skin compatible with a diagnosis of biotin deficiency. When the patient was placed on a regular ward diet, the eruption disappeared. In this unusual case, the evaluation of the effect of the lack of other vitamins is, of course, difficult.

On the assumption that egg white injury in rats may be related to seborrheic dermatitis in man, a number of investigators have tentatively administered therapeutic doses of biotin in seborrheic conditions, psoriasis, and acne vulgaris. While all these attempts have so far been futile, much more work will be necessary before a final conclusion can be made as to the role of biotin in dermatologic conditions. Schubert[486] reported encouraging results in a congenital ichthyosiform erythroderma.

Of special interest, from the viewpoint of experimental medicine, is the capacity of biotin to stimulate the carcinogenic action of certain dyes, such as butter yellow (du Vigneaud et al.[487]). Tumor tissue contains three or four times as much biotin as normal tissue, and recent evident indicates that this substance raises the incidence of certain experimental tumors in animals. Biotin promotes the deposition of large amounts of fat in the livers of animals on a diet rich in this vitamin but otherwise normal.

Biotin is derived from numerous sources, but principally from liver, kidney, yeast, and egg yolk.

The daily requirement for biotin seems to be exceedingly small. However, Gordon and Sevringhaus[347] suggest the possibility that various metabolic disorders may involve biochemical reactions tending to disturb the absorption or utilization of biotin, thus leading to a functional lack of this vitamin despite an adequate dietary intake. Whether this applies to seborrheic dermatitis and related skin conditions, as suggested by György,[449] cannot as yet be decided, but the possibility should certainly be borne in mind.

III. VITAMIN C DEFICIENCY

The role of ascorbic acid (vitamin C) in the organism's metabolism has not yet been fully established. However, the fundamental position of this

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485. Williams, R. H.: New England J. Med. **228:** 247, 1943.
486. Schubert, M.: discussion to Moncorps, C.: Zentralbl. f. Haut- u. Geschlechtskr. **54:** 290, 1937.
487. du Vigneaud, V., Spangler, J. M., Burk, D., Kessler, C. J., Sugiura, K., and Rhoads, C. P.: Science **95:** 174, 1942.

vitamin in biologic processes seems to reside in its oxidation-reduction capacity, inasmuch as ascorbic acid is readily reversibly oxidized to dehydro ascorbic acid. Commonly acting in conjunction with other reducing substances, ascorbic acid is known to perform a protective function in a variety of enzyme systems which are sensitive to environmental oxidation reduction conditions (Gordon and Sevringhaus[347]). Moreover, this vitamin appears to occupy an important position in the metabolism of certain aromatic amino acids (tyrosin, phenylalanine) and of various important compounds derived from the latter, such as melanin, adrenalin, and thyroxin (see review by Butt and associates[488]).

The most clearly established functional role of ascorbic acid is its regulatory influence on the formation and maintenance of intercellular matter, such as the collagen of all fibrous tissues, the cement substance of endothelial tissues (especially of the capillaries), the matrix of bone, and dentin and cartilage (Youmans[132]). The resorption of these intercellular substances which takes place in the absence of vitamin C explains the nature and widespread distribution of the lesions of scurvy.

The factors predisposing to vitamin C deficiency are: (1) Inadequate intake due to (a) inability to obtain vegetables and citrus fruits; (b) ignorance as to what constitutes a proper diet in regard to vitamin C; (c) use of therapeutic diets involving prolonged adherence to fruit-free regimens, as in the treatment of gastric and duodenal ulcers, gastritis, colitis, or in the presence of an allergy to citrus fruits; (d) failure to provide orange juice or its equivalent in the diet of artificially fed infants. Moreover, improper methods of storage, handling, and preparation of foods, and particularly aging, prolonged storing, or cooking, will destroy a large percentage of the vitamin C in vegetables and fruits. In aqueous solution, ascorbic acid is very sensitive to light and air. In alkaline solutions, the loss is much greater. The presence of traces of copper in cooking utensils accelerates the destruction of this vitamin.

(2) Inadequate resorption may result from gastrointestinal disturbances, notably vomiting and diarrhea.

(3) Requirements may be appreciably increased by certain diseases or by conditions which lead to an acceleration of the metabolic rate (e.g., fever, infectious diseases, hyperthyroidism, hard physical labor).

The clinical expression of severe vitamin C deficiency is scurvy. Since the general signs and symptoms of this disease are well known, they need only be summarized briefly here, while more detailed attention will be given to the cutaneous manifestations. In adults, scurvy begins insidiously with lassitude, progressive weakness, and pains in the muscles and joints. The skin is dry and scaly and of a dirty yellowish color. In

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488. Butt, H. R., Leary, W. V., and Wilder, R. M.: Arch. Int. Med.. 69: 277, 1942.

children, the sallow skin may be apparent before other symptoms make their appearance.

One of the earliest manifestations of scurvy is a follicular hyperkeratosis distributed over the buttocks and backs of the calves (Nicolau,[489] Wiltshire,[490] Scheer and Keil,[491] Hellier[492]). These lesions are sometimes termed "scorbutic goose skin" or "lichen scorbuticus." Since some doubt has been expressed as to whether these follicular hyperkeratoses may be due to concomitant vitamin A deficiency, it should be noted that the hyperkeratotic papules were the first objective findings in the cases of experimentally induced scurvy in man reported by Crandon, Lund, and Dill.[493] Nicolau[494] calls attention to the fact that the manifestations just described are sometimes the only apparent expression of mild scurvy, and that they promptly yield to ascorbic acid therapy.

Sooner or later, multiple hemorrhagic areas appear on the thighs and legs. In the classic experiment in which he was himself the subject, Crandon[493] first noted cutaneous hemorrhages on the hundred and sixty-first day of a rigidly controlled diet deficient only in vitamin C. These lesions consist of small purplish petechiae, from 1 to 3 mm. in diameter, grouped around the hair follicles. Thereafter, swelling and tenderness of the legs, as well as swelling and bleeding of the gums, may be observed. After trifling bruises, and sometimes even spontaneously, large, blue-black, bleeding lesions make their appearance on various parts of the body. As the diseases progresses, larger hemorrhages occur in the subcutaneous tissue, beneath the periosteum, and in the joints and the body cavities. The gums are raised, spongy, bleeding, and purplish (Fig. 221). At the sites of previous caries and of paradentosis the gums present a severe, deeply destructive gingivitis, closely resembling Vincent's stomatitis. However, Crandon's experiment indicates that the gums may not bleed if they and the teeth have been healthy prior to the onset of the deficiency disease.

Scurvy in infancy, which is commonly known as Barlow's disease and is encountered in artificially fed children, has its own peculiar clinical manifestations. In young patients, increased capillary fragility leads to hemorrhages not only in the skin and mucosa, but first and foremost in the bones, as evidenced by swelling of the distal end of the femur. The generally poor health of the patient is evident from his pallor, failure to gain weight (sometimes masked by edema), weakness, and irritability. In the absence of teeth, the gums show no changes. However, immedi-

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489. Nicolau, S.: Ann. de dermat. et syph. **7**: 399, 1918.
490. Wiltshire, H.: Lancet **2**: 564, 1919.
491. Scheer, M. and Keil, H.: Arch. Dermat. & Syph. **30**: 177, 1934.
492. Hellier, F. F.: Lancet **1**: 1037, 1938.
493. Crandon, J. H., Lund, C. C., and Dill, D. B.: New England J. Med. **223**: 353, 1940
494. Nicolau, S.: Bull. Acad. de med. de Roumanie **3**: 425, 1938.

ately preceding eruption of the teeth, the gums may be swollen, inflamed, and tender. If teeth are present, typical gingivitis may occur.

In the section on purpura (p. 510) a table compiled by Jeghers[322] is presented, which summarizes the pertinent features of the purpuras associated with deficiency of vitamins C, K, and P in man.

Hematologic data, with reference to bleeding and coagulation times and the blood platelets, are normal. A positive tourniquet test, with production of showers of petechiae (Rumpel-Leede phenomenon), is often seen in frank clinical scurvy (Fig. 223 on p. 481). The condition thus involves damage to the walls of the capillaries due to inadequate formation of intercellular substance.

Although frank cases of scurvy are rather rare, subclinical vitamin C deficiency is relatively widespread (Sebrell[495]). This condition may be the cause of spongy or bleeding gums, mild purpura, or a tendency to bruise readily. Other nonspecific symptoms and signs suggestive of vitamin C deficiency are vague pains in the extremities, slight pallor, anemia, weakness, and general malaise.

The relationship between subclinical vitamin C deficiency and the healing of wounds has received considerable attention. The recent work of Bartlett and associates[496] and others clearly indicates that vitamin C, in its role of promoting the formation of intercellular material, has a direct bearing on the healing of wounds. Crandon[493] reports that in himself there was a definite absence of wound healing after a hundred and eighty-three days of a vitamin C-free diet.

Another question which has been widely discussed of late is that of the connection between vitamin C and the organism's pigment metabolism. Von Szent-Györgyi demonstrated[497] *in vitro* that ascorbic acid inhibits the formation of melanin. Working along parallel lines, Schroeder and Einhauser[498] discovered that the dopa reaction is inhibited by vitamin C in tissue sections. It is interesting to note, furthermore, that the very organs which are directly connected with pigment formation, such as the adrenal and pituitary glands, contain an abundance of ascorbic acid and that destruction of the adrenal glands in Addison's disease leads to generalized hyperpigmentation. According to von Szent-Györgyi,[497] Jadassohn and Schaaf,[341] Cornbleet,[499] Abt and Farmer[500] such pigmentation responds favorably to massive doses of vitamin C. Hoff,[501] Riehl,[502]

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495. Sebrell, W. H.: J. A. M. A. **123**: 342, 1943.
496. Bartlett, M. K., Jones, C. M., and Ryan, A. E.: New England J. Med. **226**: 474, 1942.
497. Szent-Györgyi, A.: Biochem. J. **22**: 1387, 1928.
498. Schroeder, H. and Einhauser, M.: Münch. med. Wchnschr. **83**: 923, 1936.
499. Cornbleet, T.: Arch. Dermat. & Syph. **35**: 471, 1937.
500. Abt, A. F. and Farmer, C. J.: J. A. M. A. **111**: 1555, 1938.
501. Hoff, F.: Deutsche med. Wchnschr. **62**: 129, 1936.
502. Riehl, G. Jr.: Zentralbl. f. Haut- u. Geschlechtskr. **55**: 615, 1937.

and Hruszek[503] report that chloasma and other types of pigmentations yield to large doses of vitamin C and to correction of inadequate absorption of this vitamin due to gastrointestinal disorders. According to Rothman,[504] experimental evidence indicates that the beneficial effect of ascorbic acid on hyperpigmentation may be attributable to the capacity of this vitamin to reduce melanin to a lighter substance which can be absorbed. Jadassohn and Schaaf[341] are of the opinion that vitamin C exerts its influence on melanin formation indirectly, by way of the adrenals. It must be admitted, however, that we do not yet have a clear understanding of the connection, if any, between ascorbic acid and the adrenal cortex.

Further evidence of the influence of ascorbic acid on pigment metabolism is the demonstration of the need for this vitamin in order to complete the metabolism of tyrosine and phenylalanine, as seen in patients with ochronosis (Jeghers[505]). As is well known, individuals with alkaptonuria cannot completely metabolize the tyrosine and phenylalanine of their food and tissue protein, so that an intermediate product, homogentisic acid, remains. Sealock and Silberstein[506] succeeded in producing experimental alkaptonuria in guinea pigs by placing them on a diet deficient in ascorbic acid and feeding them 0.5 Gm. of l-tyrosine daily. The addition of 5 mg. of ascorbic acid caused the homogentisic acid in the urine to disappear within one or two days but it reappeared within one to three days after withdrawal of this vitamin. Similar experimental results were obtained with two normal human subjects. Alkaptonuria has also been experimentally produced in rats by phenylalanine feeding (Papageorge and Lewis[507]). From this work one must conclude that certain types of pigmentation appear to be conditioned not only by a vitamin C deficiency but also by the presence or absence of an excess of pigment precursors (Jeghers[505]).

There are other actions ascribed to ascorbic acid which may be related to its important but not fully understood function in cellular oxidation and reduction and its effects on various enzyme systems. Urbach and Kral[508] reported that protection of the skin against the effect of ultraviolet light could be accomplished by means of a combination of ascorbic acid and oil of bergamot. These observations were confirmed by Nakajo,[509] who also achieved a similar protective effect with riboflavin as well as with adrenal cortical extract in combination with oil of bergamot. Miescher,[510] on the other hand, was unable to corroborate these findings.

503. Hruszek, H.: Münch. med. Wchnschr. **84:** 1336, 1937.
504. Rothman, S.: J. Invest. Dermat. **5:** 67, 1942.
505. Jeghers, H.: New England J. Med. **231:** 88, 1944.
506. Sealock, R. R. and Silberstein, H. E.: Science **90:** 517, 1939
507. Papageorge, E. and Lewis, H. B.: J. Biol. Chem. **123:** 211, 1938.
508. Urbach, E. and Kral, F.: Klin. Wchnschr. **16:** 960, 1937.
509. Nakajo, A.: Jap. J. Dermat. & Urol. **44:** 48, 1938.
510. Miescher, S.: Schweiz. med. Wchnschr. **68:** 888, 1938.

Lever and Talbott[511] failed to observe any direct correlation between the level of vitamin C in the blood and the development of common skin diseases. Most of the cases of pemphigus, purpura, or generalized exfoliative dermatitis examined were found to have low blood ascorbic acid levels. However, this can probably be explained by the fact that most of these patients had been ill for long periods, with elevated temperatures.

The question as to whether a diet low in ascorbic acid tends to promote sensitivity, notably to arsphenamine, is still highly controversial. Sulzberger and Mayer[150] and especially Sulzberger and Oser[512] were the first to demonstrate that a diet deficient in vitamin C makes for heightened susceptibility to arsphenamine in guinea pigs and that large doses of ascorbic acid serve to inhibit such sensitization. These findings have been confirmed by Cormia[513] and refuted by Chapman and Morrell[514] and MacDonald and Johnson[515]. In man, Dainow[516] Delp and Weber,[517] and Landfish[518] have observed that untoward reactions in patients sensitive to neoarsphenamine could be prevented by injecting 100 mg. of vitamin C simultaneously with the drug. Pelner[519] reported that manifestations of sensitivity to sulfonamide compounds and salicylates could be avoided by administration of the drugs together with ascorbic acid. Other authors, however, have been unable to achieve such favorable results. These discrepancies may possibly be explained in the light of Yoshikawa's[520] observations that while guinea pigs are being allergized, small quantities of vitamin C (2–5 mg.) administered daily will increase the capacity to become allergized, but moderate doses will be ineffectual and large doses (100 mg.) will have an inhibiting influence.

The present writer found large doses of ascorbic acid (100 mg., three times daily) to be definitely beneficial during courses of parenteral therapy with gold or arsphenamine as well as during the oral administration of sulfonamides and other drugs readily causing sensitization. Holmes'[521] claim that vitamin C (500 mg. daily for one week) can control food and pollen allergies has not been confirmed despite fair trials with this approach by a number of authors, including ourselves.

Diagnosis of Vitamin C Deficiency: The patient should be examined for the characteristic signs of scurvy, as described above. In the absence

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511. Lever, W. F. and Talbott, J. H.: Arch. Dermat. & Syph. **41:** 657, 1940.
512. Sulzberger, M. B. and Oser, B. L.: Proc. Soc. Exper. Biol. & Med. **32:** 716, 1935.
513. Cormia, F. E.: J. Invest. Dermat. **4:** 81, 1941.
514. Chapman, C. W. and Morrell, C. A.: Proc. Soc. Exper. Biol. & Med. **32:** 813, 1935.
515. McDonald, F. M. and Johnson, H. H.: Arch. Dermat. & Syph. **43:** 682, 1941.
516. Dainow, I.: Presse méd. **45:** 1670, 1937.
517. Delp, M. H. and Weber, C. J.: Ann. Int. Med. **15:** 890, 1941.
518. Landfisch, S.: Polska Gaz. lek. **16:** 575, 1937.
519. Pelner, L.: New York State J. Med. **43:** 1874, 1943.
520. Yoshikawa, K.: Nagasaki Igakkai Zassi **17:** 165, 1939.
521. Holmes, H. N.: Ann. Allergy **1:** 235, 1943.

of such signs, it is well to evaluate the dietary history and determine the vitamin C concentration in the whole blood and particularly in the white cell-platelet fraction of the blood. Determination of ascorbic acid in the blood plasma and estimation of the urinary excretion of ascorbic acid are no longer regarded as reliable indices of the organism's vitamin C content. Instead, the vitamin C saturation test is being widely used at present. This procedure involves the observation, during a period of four hours, of the responses in the blood and urine to the intravenous administration of 500 mg. of ascorbic acid. In a normal individual, the typical saturation curve shows an immediate (five minute) rise in the blood level from the fasting concentration of 0.7 mg. per 100 cc. to from 4.5 to 9 mg. per 100 cc., followed by a very gradual fall from this peak. Such a curve indicates that the vitamin is not very rapidly absorbed by the tissues and infers that they contain adequate amounts of ascorbic acid. During the four hour period, 40 per cent or more of the test dose is excreted in the urine. Contrariwise, in a patient suffering from an advanced deficiency there is only a slight and variable rise (usually less than 0.4 mg. per 100 cc.) above the low fasting blood level, followed by a rapid fall, indicating the avidity of the tissues for the vitamin. The urinary excretion during this period varies from a few milligrams to as much as 20 per cent of the test dose. Lastly, the capillary resistance test (Rumpel-Leede test) will aid in the diagnosis of hypovitaminosis C, but it is not altogether dependable.

The outstanding dietary sources of ascorbic acid are fresh fruits and vegetables, particularly citrus fruits (oranges, limes, lemons, grapefruit) and the succulent and leafy vegetables. Berries constitute a rich dietary source of this vitamin, especially strawberries, currants, gooseberries, and raspberries. Tomatoes and green vegetables such as cabbage, kale, broccoli, Brussels sprouts, spinach, and water cress also provide liberal quantities. Among foodstuffs contributing an important supply of the vitamin, by virtue of the quantities usually consumed rather than the richness of their vitamin content, may be numbered apples, bananas, pineapples (canned), potatoes, green beans, and peas.

The Food and Nutrition Board of the National Research Council has recommended the following tentative daily allowance: For infants, 30 mg.; for a man of 70 Kg., 75 mg.; for a woman of 56 Kg., 70 mg.; during pregnancy, 100 mg.; during lactation, 150 mg. In acute deficiencies 200 to 500 mg. by mouth per day is required, preferably taken with the meals, since the gastric acid probably assists in absorption.

IV. VITAMIN D DEFICIENCY

Of the various chemical compounds known to possess vitamin D potency, only two are of practical importance: calciferol and 7-dehydrocholesterol.

Each of these compounds has its particular inactive precursor on which potency is conferred by either chemical or physical means. These inactive factors are: (1) ergosterol, a sterol of vegetable origin principally found in yeast and ergot, which, when activated by ultraviolet light, is converted into calciferol (vitamin D_2), known medically as viosterol; (2) dehydrocholesterol, a natural sterol of animal origin, which is present in the skin of man and animals, and which is activated by exposure to sunlight to produce a substance possessing antirachitic potency and known as vitamin D_3. The latter is found in fish liver oils, in animal fats, and in eggs, and probably constitutes the chief antirachitic substance in animal nutrition.

Vitamin D has a number of important functions with regard to human physiology. For one thing, it promotes the absorption of both calcium and phosphorus from the small intestine. Vitamin D deficiency seems to induce excessive renal excretion of phosphate, thus causing the blood phosphorus, and secondarily the blood calcium, to drop to subnormal levels (Harrison and Harrison[522]). This results in a deficient deposition of calcium salts in the growing cartilage and bone, and the calcium deficiency, in turn, constitutes the fundamental state found in rickets.

Factors predisposing to deficiency are: (1) Inadequate intake. The chief cause of vitamin D deficiency is insufficient exposure to sunlight and failure to compensate for this by the use of vitamin D preparations. While it is true that small amounts of this vitamin are present in milk, butter, eggs, and liver, it should be borne in mind that these foods alone cannot supply the required amounts of the vitamin. Adults derive the greater part of their supply through natural or artificial ultraviolet irradiation of the skin. (2) Increased requirements. The need for vitamin D is especially great during infancy, childhood, pregnancy, lactation, and certain chronic diseases.

The only commonly recognized vitamin D deficiency disease is rickets. The signs and symptoms of this disease are so well known that there is surely no need to discuss them here in any detail. However, it may be well to say a few words about the concomitant, although by no means specific, cutaneous manifestations.

In cases of advanced rickets the skin is pale, pasty, overly rich in water, and prone to infection. It is, however, thin and dry in cachectic individuals with rickets, although the latter do occasionally exhibit excessive sweating, particularly of the scalp (Monacelli[523]).

While no specific manifestations of the skin or mucous membranes are regularly seen in association with vitamin D deficiency, either in man or in experimental animals, some skin conditions definitely seem to improve

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522. Harrison, H. E. and Harrison, H. C.: J. Clin. Invest. **20:** 47, 1941.
523. Monacelli, M.: Med. Welt **11:** 1738, 1937.

under vitamin D therapy, probably because of its influence on calcium metabolism. Ceder and Zon,[524] Brunsting,[525] and Krafka[526] reported temporary improvement in a fair percentage of psoriatic patients who had been given 300,000 units of vitamin D daily. Wright[527] concluded, nevertheless, that this approach was inadvisable in psoriasis, because of the nonspecificity, high cost, and short-lived results of the treatment. Yet in cases of pustular psoriasis, a condition which is notoriously refractory to therapy, Wright[527] and Ebert[442] achieved gratifying results with intensive vitamin D therapy.

Acute vegetative and chronic cases of pemphigus will sometimes respond to daily doses of 300,000 to 400,000 units of vitamin D or of a closely related sterol (3 to 5 cc. of dihydrotachysterol), which also serves to raise the serum calcium from its low levels (Tauber and Clarke,[528] Lever and Talbott[529]). However, the improvement is only temporary and vitamin D is rarely of any value in the subsequent exacerbation (Ebert[442]). Eller and Diaz,[530] as well as the present writer, failed to observe any beneficial results.

Cornbleet and Struck[531] successfully treated eleven cases of scleroderma with daily doses of 200,000 to 300,000 units of vitamin D given over a period of nine months; and Perez et al.[532] reported satisfactory results in two patients with the same disease with daily doses of 1 cc. of dihydrotachysterol administered for some months.

According to Wright,[527] vitamin D is occasionally a helpful adjunct in the treatment of acne vulgaris but has no curative effect when given alone. Sutton and Sutton[337] have seen epidemics of acne caused by the wholesale administration of cod liver oil or its concentrates to inmates of children's homes. These authors state, however, that the effect of the oil in causing acne is attributable not to the vitamin D, but to the antagonism between the vitamin A contained in these oils and the thyroid secretion. Therefore, in dealing with acne patients, care should be taken to select vitamin D preparations of vegetable origin, such as viosterol.

In evaluating vitamin D therapy, it should be remembered that the administration of this vitamin in large doses over a long period of time may definitely involve some danger, especially in children. The calcium level in the blood should be checked at frequent intervals. It is now known,

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524. Ceder, E. T. and Zon, L.: Pub. Health Rep. **52:** 1580, 1937.
525. Brunsting, L. A.: Proc. Staff Meet. Mayo Clin. **13:** 280, 1938.
526. Krafka, J.: J. M. A. Georgia **30:** 398, 1941.
527. Wright, C. S.: Arch. Dermat. & Syph. **43:** 145, 1941.
528. Tauber, E. B. and Clarke, G. E.: Arch. Dermat. & Syph. **40:** 82, 1939.
529. Lever, W. F. and Talbott, J. H.: New England J. Med. **231:** 44, 1944.
530. Eller, J. J. and Diaz, L. A.: Urol. & Cutan. Rev. **47:** 234, 1943.
531. Cornbleet, T. and Struck, H. C.: Arch. Dermat. & Syph. **35:** 188, 1937.
532. Perez, W. M., Soffer, L. J., and Silbert, S.: J. Mt. Sinai Hosp. **6:** 333, 1940.

however, that most of the early instances of toxic effects were caused by toxic sterols associated with and related to but not identical with vitamin D. The preparations now on the market are definitely free of these toxic products.

The vitamin D requirement for a healthy normal adult human being has been difficult to determine accurately. The Food and Drug Administration has specified a daily minimum requirement of 600 I.U. for all persons, irrespective of age. For most adults no dietary source of vitamin D is required, provided there is sufficient exposure to ultraviolet irradiation as provided in daylight.

V. VITAMIN K DEFICIENCY

The term "vitamin K" refers to a group of substances of the naphthoquinone group. One of these has been assigned the name "menadione" by the Council on Pharmacy and Chemistry of the American Medical Association.

Vitamin K seems to play an indispensable role in the formation of normal amounts of prothrombin by the liver. Prothrombin, in turn, is a constituent of the blood essential to normal blood clotting. Deficiency in prothrombin (hypoprothrombinemia) results in an appreciable prolongation of the clotting time of the blood.

Factors predisposing to vitamin K deficiency are: (1) Inadequate intake. As will be seen below, a dietary vitamin K deficiency is a great rarity, for this vitamin is most probably produced by bacterial action in the intestines. The hemorrhagic disease of the newborn, however, may in occasional cases be related to an inadequate supply of the vitamin in the maternal blood.

(2) Inadequate absorption. Since vitamin K is a fat-soluble vitamin, its absorption is dependent upon an adequate supply of bile in the intestine—a fact which accounts for the tendency to increased bleeding in obstructive jaundice. A similar mechanism is involved in sprue and celiac disease due to the disordered digestion of fat in the intestine. The excessive use of mineral oil, especially when taken with meals, may prevent proper absorption of vitamin K because of its solubility in fats and oils.

(3) Inadequate utilization. In the presence of hepatic disease, vitamin K is not properly metabolized, and the result is hypoprothrombinemia.

When the blood prothrombin falls below certain levels, various clinical types of hemorrhagic disease make their appearance. Since vitamin K affects blood clotting only through its influence on the prothrombin concentration, a given case of hemorrhagic disease need not necessarily be due to a deficiency in this vitamin. The bleeding may be attributed to an underlying vitamin K deficiency only when the prothrombin concentration is abnormally low. The hemorrhagic states which are demonstrably related to a vitamin K deficiency include, notably, the bleeding which sometimes accompanies obstructive jaundice; the bleeding associated with diseases and disorders of the gastrointestinal tract, such as nontropical sprue, celiac disease, and ulcerative enterocolitis, icterus gravis and hemorrhagic disease of the newborn; and the bleeding which occurs in certain cases of nutritional deficiency.

Cutaneous purpura may reach striking proportions in vitamin K deficiency. According to Kark et al.[533] ecchymoses and blood extravasations are common and may at times cover large areas of the skin. These lesions are especially prominent on pressure areas and lack the orthostatic tendency so frequent in scurvy. As Kark and Souter[534] have pointed out, the characteristic subcutaneous hematomas or ecchymoses about needle punctures in the antecubital fossa or the ear lobe serve as a helpful guide in diagnosis. Neither generalized petechial hemorrhages nor perifollicular hemorrhages on the extremities have been observed in this condition, as in avitaminosis C (Quick[535]). Bleeding from the gums may occur after slight trauma, but the gums themselves do not present the purple sponginess characteristic of scurvy. Hemorrhagic disease of the newborn is characterized by multiple hemorrhages in the skin, mucous membranes of the mouth, stomach, intestine, and other organs.

Diagnosis of Vitamin K Deficiency: The presence of a hemorrhagic diathesis should suggest the possibility of avitaminosis K. The diagnosis depends on the presence of a low prothrombin level and prolonged clotting time. It should be borne in mind, however, that hypoprothrombinemia may also be due to primary hepatic disease, the explanation being that the damaged liver is incapable of performing the normal functions of metabolizing vitamin K and manufacturing prothrombin. Another suggestive criterion is the characteristic response of the hemorrhagic diathesis to vitamin K therapy. The bleeding time is usually normal, and capillary fragility is unaltered.

Natural vitamin K is found in alfalfa, kale, spinach, tomatoes, and soy bean oil.

The normal daily requirements of vitamin K have not been determined. The usual therapeutic dosage, both for prophylaxis and for cure of hypoprothrombinemia, is 1 or 2 mg. of menadione daily, orally or intramuscularly. When the oral route is chosen, it is advisable to accompany menadione with ox bile extract (20 to 30 grains) in order to assure proper resorption. Should the prothrombin level show a further decline in spite

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533. Kark, R., Souter, A. W., and Hayward, J. C.: Quart. J. Med. 9: 247, 1940.
534. Kark, R. and Souter, A. W.: Brit. M. J. 2: 190, 1941.
535. Quick, A.: Hemorrhagic Diseases and the Physiology of Hemostasis. Springfield, Ill.: Thomas, 1942.

of treatment, larger doses (e.g., 5 mg.) may be given by parenteral or duodenal administration, if necessary.

Most cases of hypoprothrombinemia respond to this therapy, but those which are due to liver damage show no improvement; for, as mentioned above, normal liver tissue is indispensable for the proper utilization of vitamin K and the production of prothrombin.

Newborn infants may be protected by prophylactic doses of vitamin K given the mother immediately before delivery (1 mg. of synthetic vitamin K is administered daily for three or four days prior to delivery).

Recently Black[536] reported satisfactory results with large doses of vitamin K (2 mg. three times daily before meals) in a majority of cases with chronic urticaria, particularly in those in which the prothrombin time was prolonged.

VI. VITAMIN P DEFICIENCY

Von Szent-Györgyi and his associates[537] discovered the presence of a factor other than ascorbic acid in red pepper (paprika) and in the peelings of lemons and oranges. This factor serves to lessen capillary fragility and capillary permeability and has therefore been named vitamin P (permeability factor). These authors subsequently isolated a flavone glucoside, called "citrin," from citrus fruits, which consists of two substances of the benzopyrone type: hesperidin and eriodictin.

Zacho[538] and Rusznyak and Benko[539] induced a state of lowered capillary resistance in guinea pigs and rats receiving a scorbutogenic diet which included large daily doses of pure ascorbic acid but lacked vitamin P. Administration of citrin promptly restored capillary fragility to normal.

Scarborough[540, 541] succeeded in producing isolated avitaminosis P in man. Two volunteers, who were kept on a vitamin-free diet supplemented by all the vitamins (including large doses of ascorbic acid) except vitamin P, presented a progressive increase in capillary permeability, as well as orthostatic petechial hemorrhages on the legs, in the pressure areas, and after application of a tourniquet. Since these individuals showed perifollicular petechial hemorrhages, Scarborough questions the specificity of this symptom for the clinical diagnosis of scurvy. The extensive subcutaneous hemorrhages and bleeding gums so commonly seen in scurvy did not make their appearance. Institution of vitamin P therapy relieved the purpura within forty-eight hours, and the capillary resistance progressively returned to normal. The clinical picture of avitaminosis P, as postulated by Scar-

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536. BLACK, J. H.: J. Allergy **16:** 83, 1945.
537. RUSZNYAK, S. and v. SZENT-GYÖRGYI, A.: Nature **138:** 27, 1936.
538. ZACHO, C. E.: Acta path. et microbiol. Scandinav. **16:** 144, 1939.
539. RUSZNYAK, S. and BENKO, A.: Science **94:** 25, 1941.
540. SCARBOROUGH, H.: Lancet **2:** 644, 1940.
541. SCARBOROUGH, H.: Proc. Roy. Soc. Med. **35:** 407, 1942.

borough, is therefore featured by a marked decrease in capillary resistance, perifollicular petechial hemorrhages, purpura over pressure areas, a slight increase in bleeding time, and a variety of subjective symptoms—notably pain in the legs on exertion, weakness, and fatigue.

Scarborough, who treated several scorbutic patients under similarly controlled conditions, giving vitamin P but withholding vitamin C, observed similar improvement in capillary resistance. Moreover, he found vitamin P useful in the treatment of purpura senilis.

Kugelmass[542] reported encouraging results with vitamin P in the treatment of allergic, infectious, and nutritional purpuras. Jersild[543] noted improvement in Schoenlein's and Henoch's purpura, and Miller[544] in the purpura of measles. And Gorrie[545] found this approach helpful in dealing with purpuras appearing after arsenic therapy.

Lindheimer and associates[546] arrived at the conclusion that vitamin P therapy is definitely effective in improving low capillary resistance in a variety of conditions, including some that are and others that are not of known dietary origin.

The recommended therapeutic dosage is ½ to 1 Gm. daily of citrin (hesperidin).

[542] Kugelmass, I. N.: J. A. M. A. **115:** 519, 1940.

[543] Jersild, T.: Lancet **1:** 1445, 1938.

[544] Miller, A. A.: Brit. J. Child. Dis. **38:** 1, 1941.

[545] Gorrie, D. R.: Lancet **1:** 1005, 1940.

[546] Lindheimer, G. T., Hinman, W. F., and Halliday, E. G.: J. Am. Dietet. A. **18:** 503, 1942.

CHAPTER IV

Food Allergy as Cause of Skin Diseases

Food allergy may be the cause of many and varied skin manifestations, including dermatitis (eczema), neurodermatitis, infantile dermatitis, urticaria, lichen urticatus, prurigo, purpura, and acne.

In this section we shall (1) endeavor to show, on the basis of present knowledge, just how and why sensitization takes place; (2) consider in some detail the nutritional allergens themselves; (3) discuss the diagnosis with special reference to the various methods which are available for determining the presence of a food allergy; and (4) on the basis of years of personal work, review the dietary treatment of dermatoses due to food allergy. The practical application of the principles to be presented below will be found in Part IV.

A. MODES OF ALLERGIZATION

The terms "allergization" and "sensitization" designate acquisition of the capacity to become hypersensitive, to a certain food, for example, as a result of the active production of specific antibodies. Recent investigations have shown that all individuals are potentially capable of developing allergy. Since such is the case, the question inevitably arises as to why relatively few people become hypersensitive and why an individual acquires allergy only to certain foods. So far as we know today, the answer lies in the fact that the capacity to become allergic depends upon two fundamental factors: (1) the predisposing or auxiliary conditions which pave the way for the allergy, by making the organism prone to allergization; (2) the exciting allergens, in the case of food hypersensitiveness the nutritional allergens which actually elicit the allergic reaction. The significance of such predisposing factors as heredity, the functions of the endocrine glands and of the autonomic nervous system, infections, intoxication, gastrointestinal disorders, hepatic diseases, infestations, meteorologic and climatic influences, social and environmental conditions, psychic influences, nonspecific irritations will be summarized below. For a detailed discussion of the subject, the reader is referred to the present author's textbook on allergy.[26]

The capacity of a food to become a potent antigen depends on such variables as the nature of the aliment, the quantity and concentration in which the food is ingested, and the duration of exposure. The individual capacity to become allergized to a given food is therefore the resultant of the factor of exposure to that food plus the several predisposing factors, including the individual constitution. In the vast majority of cases, sensitization to food takes place by way of the gastrointestinal tract as a result of eating allergenic food. However, before entering into a discussion of this mode of sensitization, it may be well to consider another possibility, namely, intra-uterine allergization.

According to Ratner et al.[547] the placenta, in man and rodents alike, has but one layer of connective tissue separating the maternal from the fetal blood. This tissue is permeable to antibodies and proteins. Moreover, Nathan-Larrier[548] demonstrated, with the aid of relatively small oral doses of sodium oleate, sodium ricinoleate, or bile salts, that it is possible to make the placenta permeable to antigens, without damage. This finding is of particular and of practical significance, for it explains how women may allergize the fetus to food, by taking certain laxatives or other drugs. Ratner[549] was able to demonstrate that the infant's allergy was directly due to the fact that the mother had been taking excessive quantities of milk, eggs, or other aliments during the period of pregnancy and lactation. Following their very first contact with these substances in postuterine life, these infants presented allergic reactions, such as dermatitis, urticaria, vomiting, asthma. An especially striking example is afforded by a case reported by Lyon.[550] A nursing infant, 3 months old, presented severe angioneurotic edema. The mother, a mountaineer peasant woman, had been living for years on a diet composed largely of dried white beans. The infant's edema disappeared just as soon as the beans were eliminated from the mother's diet, and promptly reappeared when the mother began eating beans again. A number of authors have demonstrated that in nursing infants the presenting dermatoses were attributable to their mothers' excessive consumption of certain food items eggs (Low,[551] Dekker[552]), milk, wheat (Ratner[549]), chocolate (Talbot), and, less commonly, bananas or nuts—during pregnancy. Elimination of the given food from the mother's diet speedily cured these cutaneous manifestations. The present writer has observed that pigs being fattened with fodder containing shredded dried fish often presented severe dermatitic lesions. The hypersensitiveness underlying these manifestations was frequently transmitted to the unborn pigs *in utero*, with the result that they developed similar dermatitides following their first ingestion of the fish preparation.

It is very difficult, of course, to prove that an infant's allergization took place *in utero* and not by way of the mother's milk. Donnally[553] demon-

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547. Ratner, B., Jackson, H. C. and Gruehl, H. L.: J. Immunol. **14:** 291, 1927.
548. Nathan-Larrier, L.: Bull. Acad. de. méd. Paris **109:** 57, 1933.
549. Ratner, B.: Am. J. Dis. Child. **36:** 277, 1928.
550. Lyon, G. M.: Am. J. Dis. Child. **36:** 1012, 1928.
551. Low, R. C.: Anaphylaxis and Sensitization. Edinburgh: Green, 1924.
552. Hansen, K., Rost, G. A., and Dekker, H.: Praktikum der allergischen Krankheiten. Stuttgart: Montana, 1930.
553. Donnally, H. H.: J. Immunol. **19:** 15, 1930.

strated conclusively that foods ingested by the mother could pass into the milk in an unaltered state. Brunner and Baron[554] confirmed these findings using cottonseed protein. Their experiments were carried out with milk specimens obtained from two and one half to twenty-four hours after the mother had taken cottonseed. Clinical cases illustrating this mechanism have been described by O'Keefe,[555] Shannon,[556] Balyeat,[557] and others. If egg, cottonseed, and other food proteins can be identified in the mother's milk, we must be permitted to assume that the moment breast feeding begins, the infant is exposed to all the antigenic foods consumed by the mother. Hence, it is not unreasonable to believe that, in certain infants, allergization may begin at birth or within a day or two thereafter. On the other hand, in cases in which the mother is known to have overindulged in certain foods during pregnancy and in which elimination of these aliments from the mother's diet is followed by disappearance of the infant's allergic manifestations, there would seem to be good reason to assume that the allergization took place through the placenta.

It should be emphasized at this point that the importance of detecting and eliminating various factors predisposing to food allergy cannot be overestimated. The current tendency to search only for the exciting allergen and to ignore the fundamental importance of the ancillary influence is unfortunate, in this writer's opinion, because such a procedure is responsible for so many failures in allergic therapy. For example, the elimination of a duly identified food is followed by complete freedom from symptoms. However, the physician is soon surprised and disappointed to see that administration of some drug brings on the same or a clinically different type of allergic reaction. But if, in addition to eliminating the specific foods the underlying predisposing factor such as chronic gastroenteritis, endocrine dysfunction, or even psychic strain is properly dealt with, the lasting freedom from the allergic disease can often be achieved. It is imperative, therefore, that the contributory conditions and the exciting agents be given equal attention from the biologic and the therapeutic points of view.

It may, of course, be even more difficult to ascertain the nature of the predisposing factor or factors in a given case of food allergy than to identify the allergenic aliment. In the first place, it is impossible to demonstrate by any known method of testing that an infection or a gastrointestinal disturbance, for example, has served as a conditioning circumstance; the results of properly directed therapeutic measures may be the only definite indication of the nature of the predisposing condition. In the second place, it must be borne in mind that a combination of two or more influences, sometimes completely unrelated but often bearing a definite relationship, is not uncommonly required to pave the way for an allergization. Thus, the writer has observed a case of food allergy in which the patient manifested her state of hypersensitiveness to a food only when she suffered from a respiratory infection during menstruation. Lastly, it must certainly be admitted that there may well be involved additional factors about which nothing whatsoever is known today.

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[554] Brunner, M. and Baron, B.: J. Allergy **13:** 358, 1942.

[555] O'Keefe, E. S.: Boston M. J. **183:** 194, 1921.

[556] Shannon, W. R.: Am. J. Dis. Child. **23:** 392, 1922.

[557] Balyeat, R. M.: Allergic Diseases. Philadelphia: Davis, 1930.

Since we consider the predisposing factors to be of fundamental significance, we feel that they merit enumeration and some discussion here:

Heredity is surely one of the major factors predisposing to allergy. However, the concept that heredity constitutes a necessary prerequisite has been definitely disproved. Moreover, critical consideration of the available evidence reveals that what is inherited is not the allergic disease itself—that is, not the clinical type of reaction but merely the allergic tendency. This would explain why, for example, a father may have angioneurotic edema due to eggs, his daughter diarrhea after drinking milk, and his son dermatitis in response to strawberries. In those relatively rare cases in which reactions occur upon first contact, there probably has been a marked exposure to the allergen at some previous time, probably *in utero*. However, there is undeniably such a thing as a highly specific hypersensitiveness to one food item that "runs" in families. This may be well illustrated by one of the writer's own cases: A patient reacted with urticaria to a single food, wild strawberries. Two of his children reacted to the same food with rather severe gastrointestinal symptoms of allergy. One grandchild presented urticaria which was again demonstrably due to wild strawberries. It is interesting to note that all of these allergic manifestations were evoked only by wild strawberries, but never by the cultivated varieties.

The importance of the *endocrine glands* in regard to the allergic mechanism is well known. Thus menstruation, the menopause, and ovarian dysfunction have often been found to be factors tending to heighten or lower the degree of hypersensitiveness. A few examples relating to food allergy may serve as an illustration. Freund[558] reported the case of a woman who invariably responded with an urticarial eruption to smoked sprats eaten during the premenstrual phase of her cycle. At other times she was able to consume an equal amount of the same food with impunity. J. Jadassohn[559] described the case of a woman who could never eat certain kinds of fruit without developing an urticarial reaction, except during her pregnancies, when she was apparently able to tolerate these items perfectly.

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558. Freund, L.: Wien klin. Wchnschr. **48:** 182, 1935.
559. Jadassohn, J.: Klin. Wchnschr. **2:** 1680, 1923.

The autonomic nervous system plays an extraordinary role as a factor predisposing to allergy. Anyone dealing with allergic patients is impressed by the high degree of vasomotor instability which they manifest. "High-strung" individuals of both sexes are more likely to be affected than are more stolid, slowly reacting persons. The marked dependence of the capacity for allergization on autonomic imbalance is probably the best explanation for the fact that ever increasing numbers of people in all walks of life are developing food allergy and other forms of hypersensitivity during the present trying times.

Disorders and diseases of the gastrointestinal tract are, of course, among the prime factors leading to allergization. Moreover, it is now known that gastrointestinal absorption of unaltered food protein is a physiologic process. This is definitely proved by: (1) demonstration of specific precipitins in the blood and urine of animals having received foreign proteins by mouth; (2) determination of specific precipitins in the blood of normal nursing infants, as well as those with pathologic intestinal conditions, following the first ingestion of cow's milk, egg white, or even vegetable protein; (3) demonstration, by the complement-fixation method, of the presence of antibodies in the blood of 60 per cent of normal, artificially fed infants (György, Moro, and Witebsky[560]); and (4) passive transfer of food hypersensitiveness by means of the Prausnitz-Kustner method using the oral route (Walzer[561]).

Physiologic resorption of food proteins may serve the purpose of maintaining within the organism a mechanism for constant deallergization in relation to protein. Under pathologic conditions, however, the degree of resorption can increase to such a point that allergization ensues. Common examples are to be found in children, especially following overindulgence in some food, such as eggs, chocolate, or bananas. The writer has also seen instances of this kind in adults following excessive consumption of one particular food. In most of these cases the newly acquired allergy expressed itself in the form of lichen urticatus. A number of these patients were country girls who found employment in delicatessen shops in the city, where they partook liberally of highly spiced sausage. A diet free of animal protein promptly relieved the symptoms. When the patients were subsequently given the same sausage in moderate quantities, there were no symptoms, which clearly indicates that excessive consumption had led to excessive resorption and thus to allergization. Similarly, animals can be allergized by repeated feeding of a protein to which they are unaccustomed (e.g., milk, eggs), on several successive days.

A significant role can also be played by an insufficiency of digestive juices, particularly by gastric hypo-acidity or anacidity, which causes the ingested food to enter the intestine too rapidly and in an inadequately digested state. Consequently, (1) there is resorption of products of incomplete digestion, and (2) as a result of insufficient bactericidal action due to the lack of hydrochloric acid, a pathologic intestinal flora may develop, which in turn provides an important factor predisposing to allergy. In achylia, the digestion of carbohydrates is also somewhat impaired, in that quantities of undigested carbohydrates enter the intestine prematurely. This may lead to diarrhea or to enterocolitis, owing to putrefaction or fermentation, and thus to chronic inflammation of the intestines with subsequent pathologic resorption of improperly digested food protein.

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[560] György, P., Moro, E., and Witebsky, F.: Klin. Wchnschr. **9:** 1012, 1930; **10:** 821, 1931.

[561] Wilson, S. J. and Walzer, M.: Am. J. Dis. Child. **50:** 49, 1935.

In many patients the writer has observed that Propeptan treatment (see p. 271) was not effective unless combined with administration of hydrochloric acid. On the other hand, hydrochloric acid without Propeptan was also ineffectual in combating the allergic dermatoses. Moreover, the writer has encountered a number of cases in which food allergy did not yield to Propeptan treatment until the coexisting enteritis was controlled by means of a diet with a low cellulose content, or an underlying putrefactive or fermentative dyspepsia was cleared up by the indicated dietary procedures (see p. 321).

Food allergies are sometimes attributable to pancreatic hypofunction. A case reported by Nathan[562] exemplifies this: A child hypersensitive to eggs presented a clinical picture of erythema and diarrhea. The stool was found to have a high content of neutral fat and poorly digested muscle fiber. During the period of treatment with pancreatin, eggs were tolerated, but the allergic symptoms recurred when the pancreatin was stopped. Renewed administration of pancreatic extract again resulted in freedom from symptoms.

Inflammations of the gastric or intestinal mucosa in the form of gastritis, enteritis, or colitis can greatly increase the resorption of undigested or inadequately digested food proteins. Leriche[563] described two cases of allergic urticaria due to meat, in which symptoms permanently disappeared following appendectomy. According to White,[564] infants suffering with colic subsequently develop infantile dermatitis three times more frequently than do normal babies.

Chronic use of alcohol and highly spiced foods can also lead to inflammation of the intestinal mucosa. Van Leeuwen[565] and the present writer have observed instances in which hypersensitiveness to particular foods manifested itself only when champagne, or other wines, and onions were taken at the same time. Gutmann[566] stresses the point that coffee, tea, spinach, and other food items which tend to increase the permeability of the mucosa can facilitate the development of an allergy. Moreover, erosions or ulcers may cause the absorption of food proteins into the blood stream.

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[562] NATHAN, M.: Bull. méd. Paris **34**: 59, 1920.
[563] LERICHE, R.: Presse méd. **44**: 916, 1936.
[564] WHITE, P. J.: Am. J. Dis. Child. **38**: 935, 1929.
[565] VAN LEEUWEN, W. S.: Verhandl. d. Ges. f. Verdauungskr. 6 Tagung. 1926.

Lastly, it should be noted that chronic constipation and intestinal atony are predisposing factors of prime importance.

Liver disorders can bring on allergization in various ways. Excessive amounts of protein can impair the proteopexic function even of a normal liver, with the result that the protein may enter the circulation and eventually cause sensitization (Dujardin and Decamps[567]). The importance of hepatic insufficiency in the production of enteral allergization has been described by Pick[568] and Yoshiynki.[569] Furthermore, the diseased liver may produce porphyrin, a substance that often induces a state of hypersensitiveness to light.

Infections and, less commonly, *infestations* may act as factors predisposing to food allergies. In this connection acute infectious diseases and chronic foci of infection are equally worthy of consideration. It has long been known that any febrile infection of the upper or lower respiratory tract, and especially any type of throat infection, may prepare the ground for a food allergy with cutaneous manifestations, or, in the event of an existing latent tendency to allergy, for a recurrence of lichen urticatus, for instance, or a shower of urticarial lesions, or dermatitis. This fact has repeatedly been confirmed in the writer's own experience, notably with regard to cases of recurrent lichen urticatus in infants and small children in whom the history has repeatedly and clearly pointed to some respiratory infection as the contributory factor in the presenting food allergy. The influence of focal infection is shown by a case reported by Kerl:[570] Following the ingestion of eggs, the patient regularly developed a papular skin eruption, nausea, and diarrhea. Exclusion of eggs from the diet brought temporary improvement. However, the food allergy was not definitely eradicated until a focus of infection in the teeth had been discovered and dealt with. Another patient presented a papular urticaria of several weeks' duration. The skin lesions had flared up after ingestion of eggs and incision of an area of periostitis. The food was tolerated, however, after removal of an infected tooth.

The pathologic flora of the intestine, especially of the colon, create one form of focal infection that has received only scant attention, probably because it generally produces no direct clinical symptoms. Nevertheless, in the writer's opinion, it plays a very important role in allergization to food. Colonic dysbacteria, as termed by Nissle,[571] is characterized by a replacement of the normal B. coli by streptococci and atypical, biologically inferior strains of colon bacilli. This condition can be demonstrated only by studying the stool bacteriologically with the aid of appropriate aerobic and anaerobic cultures. Thus, Nissle reports the case of a woman suffering from urticaria due to strawberries and fish. The stool revealed colonic dysbacteria. Therapy consisted of oral administration of viable colon bacilli (the preparation "Mutaflor" was used) and resulted in the complete replacement of the pathologic intestinal flora by normal organisms, with subsequent disappearance of the urticarial response to the foods in question. The present writer has had occasion to observe quite a few cases of this kind, which will be discussed in some detail on page 516.

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[566] Gutmann, M. J.: Münch. med. Wchnschr. **80:** 258, 1933.

[567] Dujardin, B. and Decamps, N.: Ann. de dermat. et syph. **6:** 725, 1925.

[568] Pick, E. P.: Wien med. Wchnschr. **63:** 345, 1913.

[569] Yoshiynki, H.: Scient. Rep. Gov. Inst. Infect. Dis. (Tokyo Imper. Univ.), 1922. vol. 1.

[570] Kerl, W.: Dermat. Wchnschr. **95:** 1253, 1932.

In occasional cases, infestations by intestinal worms (e.g., oxyurides, ascarides, tapeworms, echinococci) act as a predisposing factor. Thus, Adelsberger and Munter[572] reported the case of a young woman suffering from a severe dermatitis which cleared up after elimination of certain foods from her diet. The condition reappeared when she failed to adhere to the regimen. However, after successful treatment of a tapeworm infestation, the patient's intolerance disappeared completely.

Meteorologic and climatic influences play a none too clearly understood part in the production of allergic diseases in general and in the occurrence of individual attacks (Petersen and Milliken[573]). Endocrine factors and the metabolic changes occasioned by high altitudes would seem to be involved here, since it has been demonstrated that the threshold of allergic sensitivity is generally higher in the mountains. For example, the writer has observed the case of a man with manifest cutaneous hypersensitiveness to trout when he was in the city; in the mountains, however, at an altitude of some 2,700 feet, the patient was able to enjoy this fish, prepared just as it had been in town, with complete freedom from symptoms. The writer was acquainted with a physician who, for many years, had been hypersensitive to eggs, the allergy regularly expressing itself in the form of a dermatitis. During a sojourn of several weeks in the mountains, at an altitude of 3,000 feet, this allergy was not evident, but it reappeared soon after the patient's return to the city.

Social and environmental conditions can unquestionably act as factors predisposing to allergy. It is well known that those individuals who are in the intellectually and sociologically higher groups, and the urban populations in general, show a considerably greater incidence of allergies. Just why this should be the case no one really knows. Among the factors that must be considered are the hectic tempo, the excitement and tension of city life.

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[571] Nissle, A.: Münch. med. Wchnschr. 83: 1793, 1936.

[572] Adelsberger, L. and Munter, H.: Alimentäre Allergie, in Samml. zwangsl. Abhandl. a. d. Geb. d. Verdauungs u. Stoffwechs. Krankh. vol. 12, no. 5, 1934.

[573] Petersen, W. and Milliken, M. E.: The Patient and the Weather. Ann Arbor: Edwards, 1934.

The increasing artificiality of our diet due to constantly increasing use of artificial fertilizers has changed the composition of vegetables, fruits, and animal fodder in the direction of a higher content of potassium, iodine, and other elements. For example, as Sulzberger has pointed out, carrots grown with only a natural fertilizer contain 19 parts of iodine per million, while carrots grown with a certain artificial fertilizer were found to contain 2,100 parts of iodine per million. It is not unlikely that such changes in the chemical composition of common foodstuffs increase the predisposition to allergization in the organism and are thus responsible, in part, for the mounting incidence of allergy. Moreover, the wider consumption of canned foods means that the chemicals added as preservatives (e.g., acetylsalicylic acid, sodium benzoate, bisulfites) are being ingested in increasing amounts and by more and more people. Furthermore, traces of metal from the cans, small though they may be, find their way into the organism. Countless people regularly take iodized salt; and iodine, by reason of its influence on the thyroid gland, represents a possible source of allergization. The drinking water of our large cities has a high chlorine content. Flour contains considerable quantities of potassium and ammonium persulfate. These chemicals, added for the purpose of bleaching the flour and facilitating baking, are also likely to allergize the individual. The increased use of chemicals in combating pests in orchards, fields, and vineyards results in a constant increase in the quantities of arsenic and other poisons to be found in fruits, vegetables, and in wines and other beverages.

Another important reason for the rising incidence of allergy is to be found in the widespread tendency to faulty dietary habits, notably in urban centers, involving increased consumption of protein (meat, eggs), salt, and spices, as well as of food substitutes. Mention must also be made here of the increased consumption of alcoholic beverages.

In recent years *psychogenic influences* have assumed greater and greater importance, particularly during the war and the preceding period of social stress and economic depression. They include such mental factors as tension, conflict, fatigue, exhaustion, overwork, hurry, disappointment, worry, stress and strain, apprehension, fear, grief, and sex conflict. Stokes[574] has recently published an admirable presentation of this point. The literature contains a multitude of clinical examples demonstrating the capacity of psychogenic influences to pave the way for food allergies. For instance,

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574. Stokes, J. H.: Arch. Dermat. & Syph. **42:** 780, 1940.

a young woman who had never previously been hypersensitive to milk developed severe urticaria demonstrably due to this food shortly after her marriage. Profound marital disappointment was found to be the cause. When the patient was divorced, her allergy to milk disappeared completely.

It is not easy to explain the mechanisms by which psychic factors predispose to allergy. It is believed that they alter the excitability threshold of the autonomic nervous system so that stimuli hitherto of subthreshold level acquire the ability to act as excitants. Another possibility is that psychic factors may exert their influence by affecting the digestion, either by bringing about a change in the blood supply, motility, or secretion of the gastrointestinal tract or by otherwise modifying the vegetative functions of the digestive organs. For a detailed review of psychosomatic correlations in allergic conditions, with a comprehensive bibliography, the reader is referred to Stokes and Beerman.[575]

Lastly, we must not fail to mention the importance of *nonspecific irritation* as a factor predisposing to allergization to food. As pointed out above, alcohol and highly spiced foods may have a nonspecific irritative effect on the gastrointesinal mucosa. Laxatives also deserve mention in this connection. Noteworthy, too, is the fact that cutaneous manifestations of hypersensitiveness to food commonly make their appearance following consumption of iced beverages and foods, apparently owing to increased permeability of the gastrointestinal tract resulting from the effect of cold.

Before leaving the subject of sensitization to food, special mention should be made of the fact that in some instances cutaneous manifestations become evident following external contact with a nutrient as well as after its ingestion. Templeton[576] has reviewed the literature and added several of his own cases of this kind. That type of sensitization which is caused by external contact expresses itself in the form of epidermatitis, a newer name for the German word "eczema"; here the epidermis is the shock tissue. Sensitization following ingestion of food and causing dermatitis is induced by reaction of the dermal vessels to food allergens which have been absorbed by way of the digestive system. The simultaneous epidermal and dermal sensitization is of special interest because of the different shock tissues involved: the epidermis in the former case, and the dermis or, more correctly, the vessels of the dermis in the latter.

B. FOOD ALLERGENS

All foodstuffs and beverages, with the exception of water, can act as nutritional allergens in a given case. Even water, when taken too cold, can elicit a reaction in the form of cold urticaria; and if chlorine has been added to the water, individuals hypersensitive to that chemical will respond with allergic manifestations.

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[575] Stokes, J. H. and Beerman, H.: Psychosom. Med. 2: 438, 1940.

[576] Templeton, H. J.: J. A. M. A. 127: 908, 1945.

It must be stressed that an allergy need not necessarily be due solely to animal or vegetable proteins, but that there are occasional cases of hypersensitiveness to carbohydrates or fats. Furthermore, Urbach and Willheim[577] have demonstrated allergy to certain salts and acids present in the food; and Urbach and Wiethe[578] have observed cases of specific hypersensitiveness to volatile oils from ingested lemon or orange peel.

Food allergy can manifest itself in the skin in the form of dermatitis (eczema), neurodermatitis, urticaria, angioneurotic edema, lichen urticatus, pruritus, fixed pigmented erythema, purpura, erythema multiforme, dermatitis herpetiformis-like eruptions, and acne vulgaris. Needless to say, only a certain percentage of these skin diseases is due to hypersensitiveness. Moreover, the allergic etiology is quite rare, as far as acne vulgaris is concerned. A full discussion of these relationships will be found in Part Four.

While the more important food allergens will be discussed below we shall here present some observations of a general nature intended to explain why it is sometimes so extraordinarily difficult to identify the nutritional allergen or allergens in a given case.

Because a hypersensitiveness may occur only in reaction to a certain kind of given foodstuff or to a particular combination of a number of foods, even food trials may be fallacious. Thus, Pagniez[579] described a case of an individual who was allergic only to strawberries grown in a certain Swiss canton. Vaughan[580] reported that a man who could tolerate celery grown in Florida reacted to that grown in Colorado, and that another individual manifested responses to Florida but not to California oranges. In Sticker's[581] patient the allergic manifestations appeared after ingestion of honey from linden blossoms, while heather honey could be eaten with impunity. Balyeat[582] has shown that sometimes intolerance to milk is due not to hypersensitiveness to the milk protein itself but rather to substances the animal has eaten in its feed, tracés of which have gone into the milk. The situation is sometimes even more complicated than this, as in Duke's[583] patient in whom asthmatic attacks followed ingestion of roasted and salted peanuts, whereas there was no response to peanuts that had been roasted and not salted, or salted and not roasted.

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[577] Urbach, E. and Willheim, R.: Klin. Wchnschr. **11:** 1012, 1932.

[578] Urbach, E. and Wiethe, C.: München. med. Wchnschr. **78:** 2030, 1931.

[579] Pagniez, P.: Nouveau Traité de méd. et therapeutique. fasc. vii.

[580] Vaughan, W. T.: Discussion to Sulzberger, M. B. and Simon, F. A.: J. Allergy **6:** 55, 1934.

[581] Sticker, G.: Das Heufieber und verwandte Störungen. Vienna: Hoelder, 1912.

[582] Balyeat, R. M.: J. Allergy **1:** 516, 1930.

[583] Duke, W. W.: Asthma, Hay Fever, Urticaria, and Allied Manifestations of Allergy. St. Louis: Mosby, 1926. 2nd ed.

In occasional instances, however, the specificity depends not only on the substance itself, but on the method used in preparing it or on the combinations of food eaten. Rowe[584] observed cases of hypersensitiveness to fruit in which cooked fruit was not tolerated, while raw fruit was eaten with impunity—an observation which, according to Adelsberger and Munter,[572] is especially applicable to plums. Vaughan,[585] on the other hand, reported an individual in whom raw pears evoked allergic manifestations and cooked pears did not. Similar observations have been made in regard to other foods, including eggs and fish.

Particularly interesting are the cases in which only a given combination of foods, but none of the ingredients individually, acted as an allergen. Thus, Duke[583] cited a patient who tolerated both raw and cooked eggs, but responded with allergic manifestations to traces of egg in cake or cooked noodles. The writer treated a nurse who reacted with severe itching and papules to an omelet but was able to tolerate raw and cooked eggs, milk and flour when these food items were ingested separately. Similarly, Dekker[552] described severe skin manifestations in a woman following ingestion of a porridge composed of oatmeal and milk, but this patient tolerated both oatmeal and milk perfectly when they were taken alone. Ratner mentioned two similar instances: the first showed hypersensitiveness to chocolate and strawberries, but would react only when both were eaten at the same time; the second, an individual sensitive to lobster and corn, suffered no reactions when either of these two items was eaten separately.

Since the precise origin of food, the mode of preparation, and the combination of foods eaten are important points in some instances, it is imperative that diet trials be made under conditions identical with those of the patient's exposure—that is, with the food or foods just as they were originally ingested by the patient.

Certain diagnostic difficulties are also presented by the fact that often an allergic reaction does not appear promptly after the food trial test is made. Sometimes the reaction fails to appear until twenty-four hours later (Laroche, Richet, and Saint-Girons;[586] Cooke,[587] Urbach). Vaughan[588] reported the case of a woman whose migraine attack always set in precisely thirty-six hours after ingestion of chocolate. This makes it easier to understand why a nutritive urticaria, for example, does not always disappear promptly after one day's avoidance of the food that causes it.

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584. Rowe, A. H.: Clinical Allergy due to Food, Inhalant and Other Causes. Philadelphia: Lea & Febiger, 1937.
585. Vaughan, W. T.: J. Allergy 1: 385, 1930.
586. Laroche, G., Richet, C. Jr., and Saint-Girons, F.: Arch. de méd. exper. et de anat. path. 26: 51, 1914.
587. Cooke, R. A.: Ann. Int. Med. 3: 658, 1930.
588. Vaughan, W. T.: Practice of Allergy. St. Louis: Mosby, 1939.

Pagniez and Coste[589] reported that an urticarial response in a woman hypersensitive to bread reached its maximum as late as several days after she first began to eat that food, and did not begin to decline until some twenty-four to forty-eight hours after its elimination from the diet. Rowe[584] has pointed out that, particularly in hypersensitiveness to fruit, the appearance of skin manifestations may sometimes be delayed for several days and may persist despite thorough cleansing of the intestinal tract.

When the reaction to a nutritional allergen is delayed for a number of hours, one of the following conclusions may be drawn: (1) the allergen is absorbed not in the upper but in the lower part of the digestive tract; (2) the allergen is not the unaltered food, but is either a product of digestion or is a secondary antigen (produced, for example, by the action of intestinal bacteria on the food protein). In the section on predisposing factors in food allergy we have attempted to explain the mechanism underlying those cases in which a nutritive agent becomes endowed with allergenic properties only when a local predisposing condition, such as gastritis or colitis, coexists.

In this connection the important observations of Alvarez and Freelander[590] on the rate of progress of food residues through the bowel may be cited. Thus, when fifty glass beads were given to normal subjects, Alvarez observed that 15 per cent were passed the first day, 40 per cent the second, 15 per cent the third, and 10 per cent the fourth. However, the rate of progression varied widely even in healthy persons, some of whom took a week or more to pass 70 per cent of the beads.

It sometimes happens that a food hypersensitiveness appears only during the hay fever season. This has not yet been adequately explained. There is a possibility that as result of a severe pollinosis there is a general lowering of the threshold of tolerance, including that to the allergenic food. In the same category belong those cases in whom a food will cause trouble only when the organism has been allergized by some adverse influence such as fatigue, menstruation, or the inhalation of dusts. In other words, two factors may produce symptoms when one alone is not sufficient to do so (Alvarez[591]).

Quite a different problem—i.e., food allergy as a predisposing factor to other hypersensitivities—is presented by Vaughan's[588] patient who could eat strawberries and tomatoes with impunity as long as he avoided sunlight, but in whom, following ingestion of these two food items, exposure to sunlight regularly brought on eruptions in the unprotected skin areas. Sunlight alone was tolerated perfectly. Similarly, Gougerot[592] reported

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589. Pagniez, P. and Coste, F.: Bull. et mém. Soc. méd. de. hôp. de Paris **48:** 1368, 1924.
590. Alvarez, W. C. and Freedlander, B. L.: J. A. M. A. **83:** 576, 1924.
591. Alvarez, W. C.: Nervousness, Indigestion and Pain. New York: Hoeber, 1943.
592. Gougerot, H.: Bull. Soc. franc. Dermat. **37:** 1162, 1930.

the appearance of a dermatitic eruption of the face, the front of the chest, and the forearms and hands (i.e., the areas exposed to the sun) following ingestion of a certain cheese. All these cases are examples of light hypersensitiveness in which nutritional allergy is the predisposing factor.

Paul Gross[593] observed the sudden onset of what appeared to be physical urticaria in his 2 year old son. When the child was taken out for a walk in cold weather, urticarial wheals appeared on the uncovered areas of his skin. This was found to be due to a certain brand of gelatin dessert; when he was given another type, he could be exposed to cold with impunity, but the urticaria recurred as soon as the first gelatin dessert was deliberately reinstated. In this case, the food allergy predisposed to hypersensitiveness to a physical agent (cold).

Determination and elimination of the predisposing nutritional allergens is imperative in such cases as a requisite to the management of the hypersensitiveness to the second antigen (e.g., cold, light).

It must be remembered, furthermore, that a case of hypersensitiveness to a food may present a quantitative problem. Thus, many patients can tolerate an allergen—egg or milk or chocolate, for example—when taken in small quantities for a day or two, though allergic symptoms will be elicited within the next few days by the cumulative effect of the allergen. As pointed out by Alvarez,[591] another difficulty is presented by those individuals who can eat a mildly allergenic food without reactions twice a week but not every day.

Lastly, it should be noted that patients are relatively rarely hypersensitive to one food item alone. In occasional cases, the allergy is directed against a particular group of nutrients all of whose members are related biologically or chemically, for example, every kind of meat, or every kind of milk. As a rule, however, the allergic individual is hypersensitive to a number of completely different foods for instance, eggs, carrots, spices, and salt (see Figs. 175, 176, p. 431).

The principal nutritional allergens will be briefly discussed below. For obvious reasons, we shall not endeavor to incorporate every pertinent observation in this discussion.

1. Proteins of Animal Origin

In animal foodstuffs, antigenic properties are possessed almost exclusively by the proteins. *Fish* and *seafood* seem to be in the forefront of this category. The marked hypersensitiveness to cooked fish reported by Prausnitz and Küstner[594] has become famous because, in the course of their investigation, the authors discovered the invaluable passive transfer test

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593. Gross, P.: Personal Communication.

594. Prausnitz, C. and Kuestner, H.: Zentralbl. f. Bakt. **86**: 160, 1921.

method which bears their names. Of course, the hypersensitiveness is not always directed only against cooked fish protein but also to raw fish. Symptoms may often be elicited by minute traces of fish protein, as, for example, the infinitestimal particles of fish skin commonly used to clear coffee in Norway and similarly used in France to clear cheap white wine, as well as the traces of protein remaining in cod liver oil. How high the degree of hypersensitiveness to fish can be is shown by those cases in which the mere odor of fish causes swelling of the eyelids and conjunctivitis (Kaemmerer[595]), sometimes even angioneurotic edema over the entire surface of the skin (Lewis and Grant[596]), acute dermatitis (Fig. 59), or urticaria, purpura (Fig. 60), and asthma as observed by Boss[597] and the present writer. Allergic skin manifestations have been reported following ingestion of such fresh and salt water fish as eels, salmon (sometimes only when smoked), mackerel, lake fish, and various smoked fish. Rowe[598] described an instance in which small vesicles around the mouth and on the buccal mucosa, as well as nausea, vomiting, and abdominal pains, were brought on by a dish of trout. Sachs[599] has reported four cases of purpura due to anchovies. Particularly noteworthy, in this respect, are mussels and other mollusks, especially in the summer. To be sure, it is often difficult to determine, in a given case, whether one is confronted with a food allergy or with a condition caused by toxic products resulting from food spoilage due to heat. Oysters are very dangerous, especially at spawning time. And other kinds of seafood, such as lobsters, crawfish, shrimps, crabs, snails, and so on, must also be regarded with suspicion. Hypersensitiveness in the same person to all kinds of fish or seafood is

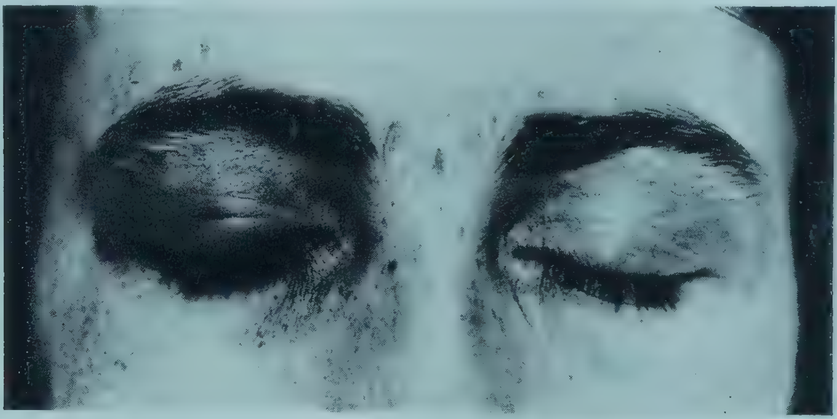

FIG. 59. ACUTE DERMATITIS WITH SWELLING OF EYELID DUE TO HYPERSENSITIVENESS TO FISH

very rarely encountered, the allergy being generally directed against one or more species. The specificity may be so great that, in occasional cases, the patient will react only to Norwegian sardines, for example, and not to sardines of any other origin; or he will respond violently to crawfish, but tolerate lobster perfectly.

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[595] KAEMMERER, H.: Allergische Diathese und Allergische Erkrankungen. Munich: Bergmann, 1926.

[596] LEWIS, T. and GRANT, R. T.: Heart **13:** 219, 1926.

[597] BOSS, A.: Arch. f. Dermat. u. Syph. **162:** 454, 1930.

[598] ROWE, A. H.: J. Lab. & Clin. Med. **13:** 31, 1927.

[599] SACHS, O.: Arch. f. Dermat. u. Syph. **123:** 835, 1916.

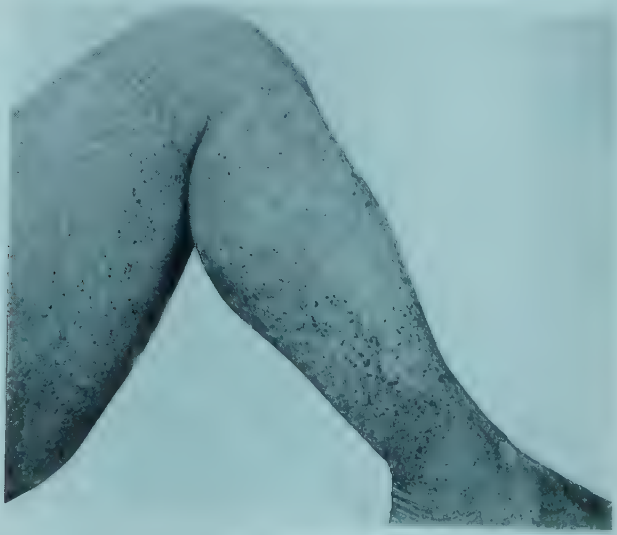

FIG. 60. PURPURA ON THE BASIS OF HYPERSENSITIVENESS TO SHAD

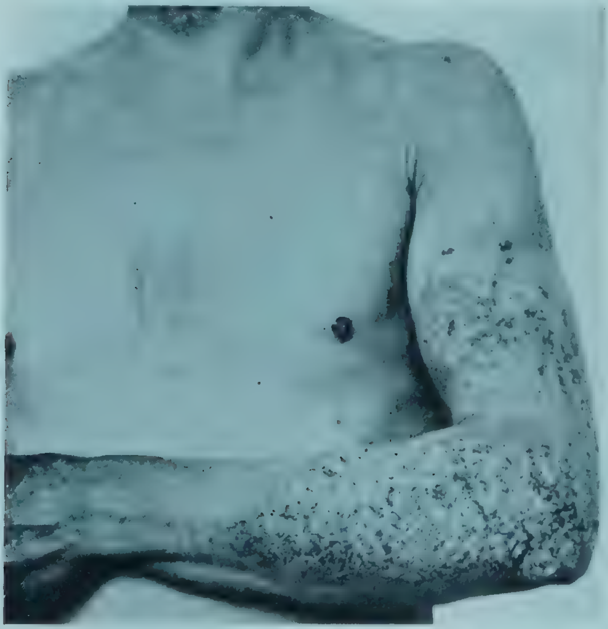

FIG. 61. WEEPING, CRUSTING, RECURRENT DERMATITIS OF THE EXTENSOR SURFACES OF THE ARMS CAUSED BY HYPERSENSITIVENESS TO PORK

Every known kind of *meat* is capable of allergenic action. Pork (Fig. 61) heads the list followed by beef, veal, lamb, mutton, rabbit, chicken, turkey, pigeon, duck, goose, and venison. On more than one occasion, the writer has been able to demonstrate hypersensitiveness to horse meat. In this connection, it is particularly interesting to note the observations of Hanhart[600] and others that individuals who have been eating horse meat for some time may exhibit severe primary reactions to injections of horse serum. Sausage, ham, and other prepared meats deserve special mention as nutritional allergens, although it is to be noted that the causal agent is not always the animal protein itself, but occasionally the added ingredients (salt, pepper, or saltpeter) or the intermediary products resulting from the smoking process. The allergenic effects which sometimes appear to be due to lard, bacon, goose fat, and other shortenings of animal origin are attributable in the great majority of cases to traces of meat adhering to the fat. The percentage of cases of true allergy to fat is very small indeed.

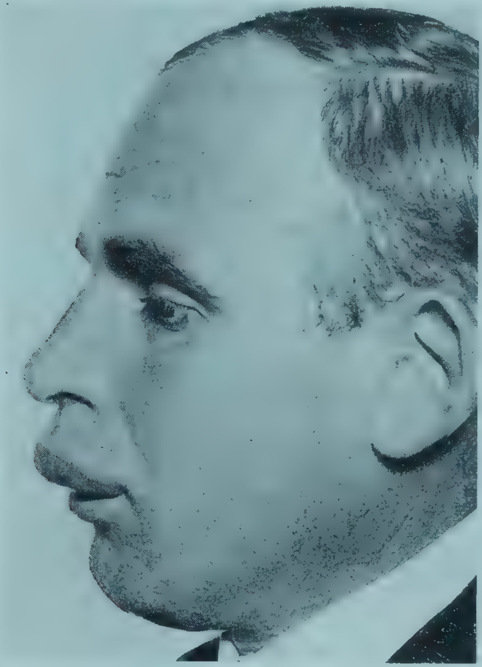

FIG. 62. ANGIONEUROTIC EDEMA OF THE UPPER LIP INDUCED BY EGG ALLERGY

Group sensitivity is not very common. As a rule, the hypersensitiveness is directed against only one or two of the meats most frequently eaten.

It is noteworthy that in cases of hypersensitiveness to the flesh of a particular animal, the liver, sweetbreads, kidney, and brain of that same animal may be eaten with impunity. Of course, the reverse has also been observed. The writer has seen cases in which severe urticaria followed ingestion of beef or chicken liver, although the meats of these animals were tolerated. In other words, this allergy was organ-specific and not species-specific.

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[600] HANHART, E.: Deutsche med. Wchnschr. **63:** 1753, 1937.

Meats are not infrequently the cause of cutaneous manifestations, generally in the form of dermatitis or urticaria, but occasionally of purpura as well.

Certain common sources of error due to failure to realize the presence of small amounts of meat protein should be pointed out here. Lard is often used in the preparation of other shortenings; nearly all canned soups, including vegetable and chicken soups, contain beef; veal is commonly used as a substitute in chicken salad; and gelatin has traces of native protein.

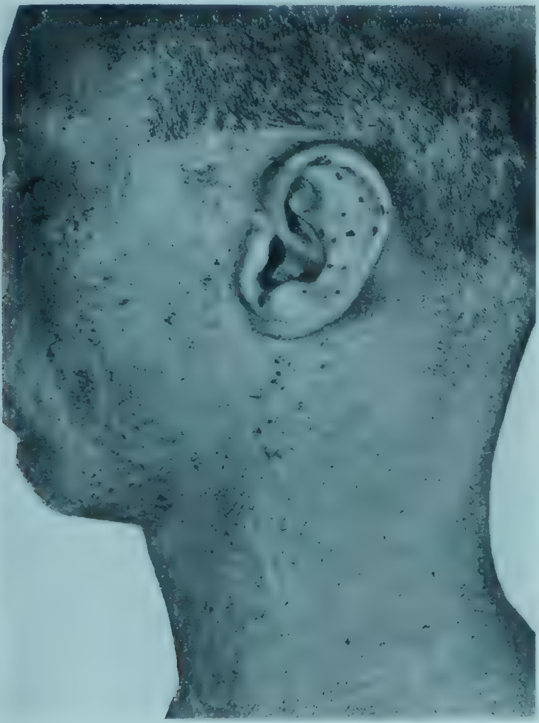

FIG. 63. NEURODERMATITIS BASED ON HYPERSENSITIVENESS TO EGG

Hypersensitiveness to *eggs* is even more common than hypersensitiveness to fish and meat. Generally speaking, eggs seem to elicit cutaneous manifestations more frequently than they do other allergic symptoms, particularly dermatitis, urticaria and angioneurotic edema (Fig. 62). Moreover, in contrast to many other food allergens, egg white produces reactions very rapidly. On the other hand the author was able to trace cases of severe neurodermatitis of long standing to this allergen (Fig. 63). Egg protein is most active allergenically when raw; in fact, the intolerance is sometimes restricted to eggs in the raw state (Pagniez, Vallery-Radot, and Haguenau[601]), but as a rule the patient reacts to cooked egg protein as well. It is only in a truly exceptional case that egg white is tolerated

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601. PAGNIEZ, P., VALLERY-RADOT, P., and HAGUENAU, J.: Bull. et mém. Soc. méd. d. hôp. de Paris 37: 1077, 1921.

raw but not when cooked. Far less common are cases of hypersensitiveness to egg yolk alone (Castaigne and Chiray), and here again there are instances in which only raw egg yolk (Parisot and Simonin), and others in which only cooked egg yolk, elicit allergic reactions.

A number of pertinent observations will be presented in the chapters on dermatitis and infantile dermatitis, where the significance of positive skin reactions to egg white will be discussed in detail. Here mention will be made only of those cases in which the hypersensitiveness was of such a high degree that mere external contact with egg white incident to opening eggs sufficed to cause urticarial eruptions on the hands (Joltrain,[602] Brabant[603]) or in which anaphylactic attacks were brought on merely by the presence of the patient in a room in which an egg was being opened (Sutton[603a]). The writer knows a 12 year old boy who immediately reacts with an urticarial swelling of the buccal mucosa, vomiting, and diarrhea whenever he eats bread sliced with a knife that has been previously used to cut up an egg. In the light of such observations, it is not difficult to understand why a highly hypersensitive nursing infant should respond with allergic manifestations to its mother's milk, when the mother has previously eaten eggs.

It is imperative, therefore, to know just what dishes are prepared with eggs or are likely to contain traces of egg. As already mentioned, the minutest quantities can evoke reactions of the greatest severity in hypersensitive individuals. For a list of foods and beverages containing egg, see "Prohibited Foods" in Table 50, on page 246.

Another nutrient which deserves special attention, notably in dealing with children (Fig. 64) but also in adults, is *milk* and its products. A few examples may serve to illustrate its importance. Hazen[604] reported the case of a 19 year old girl who had been suffering from neurodermatitis since she was 1 year old, with the exception of a period of time spent on a small island where there was no milk whatsoever. Experimental food trials showed that minute quantities of cream sufficed to bring on a recurrence of the skin condition, and that the patient's skin remained free from symptoms so long as milk was rigorously excluded from her diet. Robinson[605] saw an infant's intensely pruritic dermatitis vanish completely on a milk-free diet and discovered that a recurrence of the cutaneous condition was due to ingestion of bread that had been prepared with milk. Similar observations have been reported by Baagö[606] and other authors.

Most patients are affected only by raw or pasteurized milk, but others

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602. Joltrain, E.: Les Urticaires. Paris: Doin, 1930.
603. Brabant, V. G.: Bull. et mém. Soc. méd. d. hôp. de Paris **47:** 1302, 1923.
603a. Sutton, R. L.: Discussion to Pels, I. R.: Arch. Dermat. & Syph. **16:** 639, 1927.
604. Hazen, H. H.: Arch. Dermat. & Syph. **18:** 121, 1928.
605. Robinson, H.: Arch. Dermat. & Syph. **16:** 638, 1927.
606. Baagö, K. H.: Zentralbl. f. Haut- u. Geschlechtskr. **20:** 52, 1926.

are allergic to heated milk as well. Ratner and Gruehl have shown that the loss of antigenic properties in boiled milk is due to the coagulation of the whey proteins. This explains why a good percentage of individuals react to raw but not to boiled milk. The degree of hypersensitiveness may be so extreme that swelling of the tongue and lips is seen to result from drinking one drop of milk diluted with water (Schloss). Such observations help to explain why many individuals who are allergic to milk also respond with symptoms to butter which is known to contain only a very low percentage of protein.

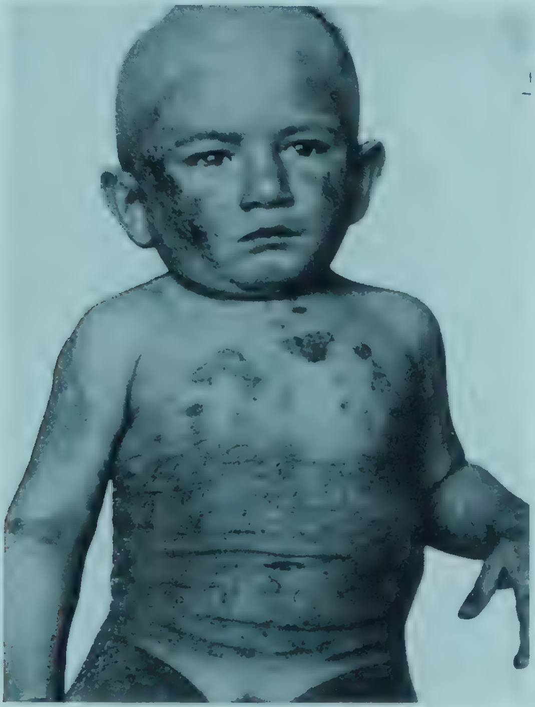

FIG. 64. EXTENSIVE DERMATITIS IN A CHILD OF 18 MONTHS DUE TO MILK ALLERGY

While milk contains four proteins, only the lactalbumin and, far less frequently, the casein are of importance in milk allergy. When the hypersensitiveness is a reaction specifically to the lactalbumin, the patient who cannot tolerate cow's milk, for example, can drink goat's or sheep's milk with impunity. But this is not the case in instances of hypersensitiveness to casein, for, as Wells[607] has shown, casein from the milk of an animal of any given species shows a closer biologic relationship to the casein of another species than it does to the whey proteins.

Although it is true that almost all reports refer to hypersensitiveness to cow's, sheep's, goat's, or mare's milk, symptoms of which usually appear after the infant has been weaned, there have been a few reports of allergy exclusively to human milk (Richet[608]). In such cases, however, appropriate control tests must be performed to confirm the assumption that the hypersensitiveness is in reaction to the mother's milk itself. This is necessary because there is always the possibility that the infant may be allergic to some food or drug ingested by the mother, traces of which are secreted into the milk. In this connection it is interesting to note Balyeat's observation[582] that a child allergic to wheat gave dermatitic response to cow's milk only when it came from cows that had been fed bran; milk from animals on green fodder was tolerated perfectly.

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[607] WELLS, H. G.: Chemical Aspects of Immunity. New York: Chemical Catalogue Co., 1929. 2nd ed.

Individuals who are hypersensitive to the lactalbumin of milk cannot tolerate cheeses prepared from whey, such as cottage cheese and cream cheese. Individuals allergic to casein, on the other hand, react to cheese that consists primarily of casein or the curd fraction—i.e., American, Edam, Gorgonzola, Parmesan, Roquefort, and Swiss cheeses. In occasional instances, however, the hypersensitiveness is not a reaction to the milk protein in the cheese but to the molds that ripen it; this is especially the case with Camembert and Roquefort varieties.

Milk, like eggs, is to be found in many foods in which its presence would not be suspected by the uninitiated. For a list of foods and beverages containing milk, see "Prohibited Foods" in Table 51 on page 247.

2. Proteins of Vegetable Origin

The allergenic factors in foods of animal origin are, in the light of our present knowledge, almost exclusively proteins, but it has been proved that a number of other substances (carbohydrates, fat salts, acids, and spices) can also be the active agents in cases of hypersensitiveness to vegetable foodstuffs. Further investigation will be required to determine whether allergenic actions can be exerted by chemical substances of nonprotein nature as such or only when conjugated with the protein. In the protein-conjugate form such substances are termed haptens. The hypersensitiveness which may follow ingestion of vegetable foodstuffs is occasionally a reaction to added substances, as, for example, the green coloring matter used for staining gelatin. This dye contains 2.6 per cent of aniline color (Baer[609]).

a. Cereals

Wheat acts as a nutritional allergen in children and adults alike, generally evoking reactions in the form of lichen urticatus, urticaria, or dermatitis. Figure 65 presents characteristic allergic responses to wheat. In the great majority of cases the hypersensitiveness is directed specifically against wheat; rye, corn, and other cereal grains are tolerated. Needless to say, instances of group hypersensitiveness to many or all flours are also encountered now and then. Some wheat is eaten at virtually every meal. For a list of foods containing wheat, see Table 52, page 248.

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[608] Richet, C.: Cited by Laroche, G., Richet, C. Jr., and Saint-Girons, F. in Alimentary Anaphylaxis. English edition by M. and A. Rowe. Berkeley, 1930.

[609] Baer, H. L.: J. A. M. A. **103:** 10, 1934.

Hypersensitiveness to *rye* occurs more frequently in Europe than in America, owing to the fact that, in general, rye is eaten more extensively there. It is interesting to note the observation reported by Benjamins and by Gutmann that hay fever patients with hypersensitiveness to rye pollen respond to the ingestion of rye bread with hay fever manifestations, which disappear when this type of bread is eliminated from the diet and reappear when it is again eaten.

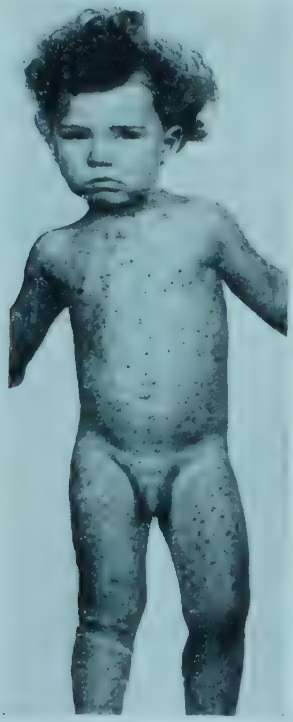

FIG. 65. LICHEN URTICATUS DUE TO WHEAT ALLERGY

Corn is a not uncommon cause of allergy (Fig. 66). Although corn flour is used in many breads, it is more extensively eaten in the form of corn meal or as hominy, polenta, and prepared cereals. Cornstarch is widely employed in desserts and as a thickening for soups, gravies, and sauces. Moreover, corn sugar and corn syrup are extensively used in the manufacture of canned fruits, preserves, jams, jellies, chewing gum, confections, candy bars, ice creams, and commercial gelatin desserts. Finally, corn oil is frequently used as shortening. *Barley* is found in children's foods, coffee substitutes, soups, and above all in the manufacture of malt and beer. *Oats* are widely eaten in the form of oatmeal, particularly as a breakfast food, but also in prepared crackers and wafers. *Rice* is rarely an offender; however, Talbot[610] and Rowe[598] have reported dermatitis and urticaria in occasional cases.

Mention must be made here of other plants which, although not included among the cereals from the botanic point of view, are used either alone or, more frequently in combination with wheat, corn, and other flour in the preparation of bread, cakes, and proprietary food products. *Buckwheat* allergy is relatively rare, but it can be extraordinarily severe. It is advisable, therefore, to be cautious in carrying out skin tests with buckwheat. Hypersensitiveness to *flaxseed* cereal must also be mentioned here. Flaxseed is present in Roman Meal and in Uncle Sam's Health Food Vaughan[588] has reported the case of a woman who was so allergic to flaxseed that she responded with angioneurotic edema of the tongue and of the oral mucosa to the first mouthful of flaxseed cereal. Bowen and Walzer observed manifestations of flaxseed allergy brought on by drinking milk from cows that had been fed flaxseed meal.

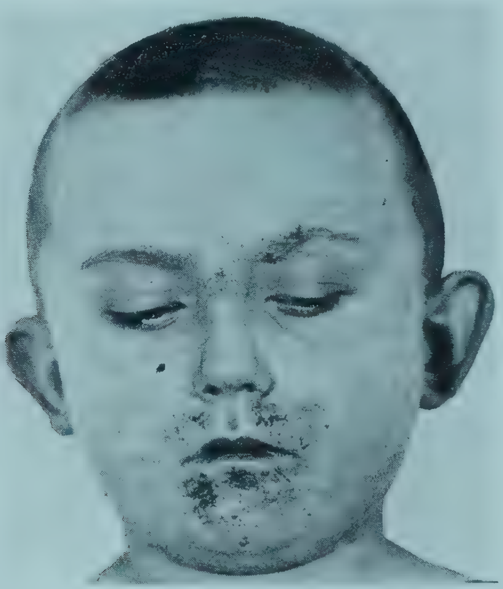

FIG. 66. CIRCUMORAL ALLERGIC DERMATITIS INDUCED BY EATING CORN

Finally, there is *soy bean* flour, which is being used more and more as a substitute for other kinds of flour, largely because of its high protein and fat content and its extremely low carbohydrate content. A strained aqueous suspension of the pulverized beans looks like milk and is successfully employed as a milk substitute for patients allergic to cow's milk, in children as well as adults. Furthermore, soy bean flour is often employed in combination with wheat flour for the preparation of cakes,

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610. TALBOT, F. B.: Boston Med. & Surg. J. 179: 285, 1918.

macaroni, and crackers, as well as in sauces, coffee substitutes, and other foods.

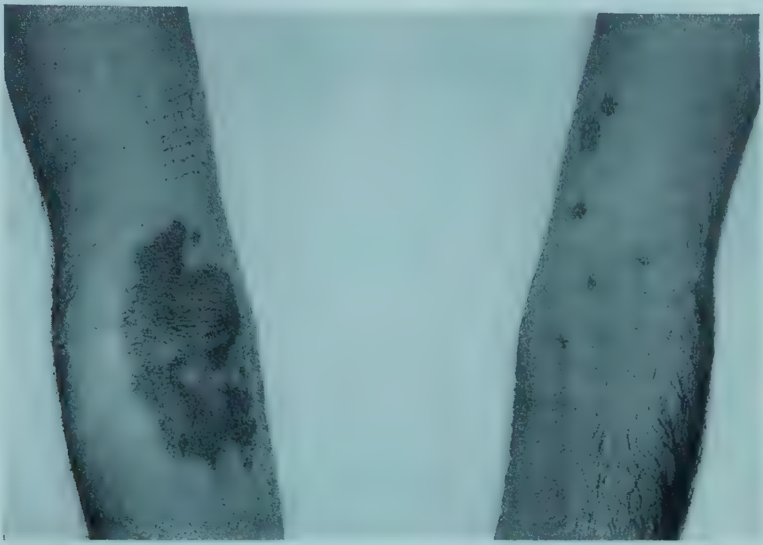

Fig. 67. Fixed Exanthem Due to Hypersensitiveness to Lentils
Lesions were indistinguishable from fixed drug eruption in appearance.

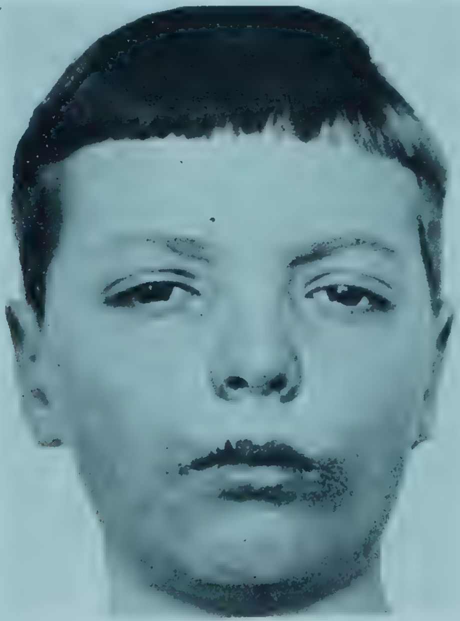

Fig. 68. Cheilosis and Circumoral Dermatitis Resulting from Spinach Allergy

b. Vegetables, Fruits, and Nuts

Hypersensitiveness to *vegetables* is far more common than the literature would seem to indicate. It may be said that there is no vegetable that has not at one time or another been the demonstrable cause of an allergy.

Most commonly encountered, however, and probably also the most severe, are cases of hypersensitiveness to the legumes (peas, beans, soy beans, lentils (Fig. 67), peanuts). Then come, in approximate order of frequency, tomato, carrot, spinach (Fig. 68), cabbage, asparagus, rhubarb, celery, onion (Fig. 69), and garlic. Occasional observations concern sweet potato, cauliflower, cucumber, turnip, pumpkin, and squash.

Those vegetables which are obtainable fresh only at certain times of the year can bring on seasonal symptoms; those which are always available must be taken into account all through the year. The same considerations apply to fruits.

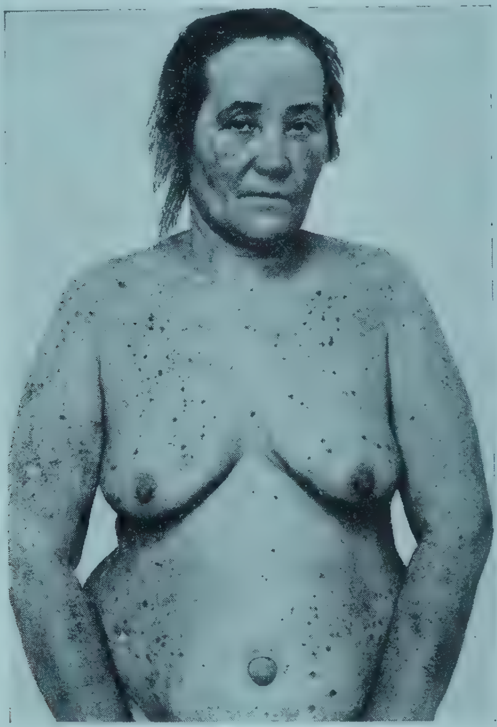

FIG. 69. PRURITUS DUE TO ONION HYPERSENSITIVENESS

Occasional cases have been reported in which the patient is allergic only to the raw and not to the cooked vegetable, and vice versa.

Skin tests are notoriously misleading in cases of hypersensitiveness to vegetables and fruits. The results are very frequently nonspecific, or they may show group reactions. For example, there may be positive reactions to all legumes in the presence of a clinical allergy to peas alone. On the other hand, in many cases of allergy, skin tests with stock vegetable extracts are consistently negative, while those made with fresh extracts are positive (Tuft and Blumstein,[611] Cooke[612]).

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611. TUFT, L. and BLUMSTEIN, G. I.: J. Allergy 13: 574, 1942.
612. COOKE, R. A.: J. Allergy 15: 203, 1944.

Among the *fruits*, strawberries (Fig. 70), bananas, oranges (Fig. 71), grapes, and apples are the principal offenders. There has been occasional reports, however, of hypersensitiveness to pears, cherries, plums, raspberries, gooseberries, and other fruits.

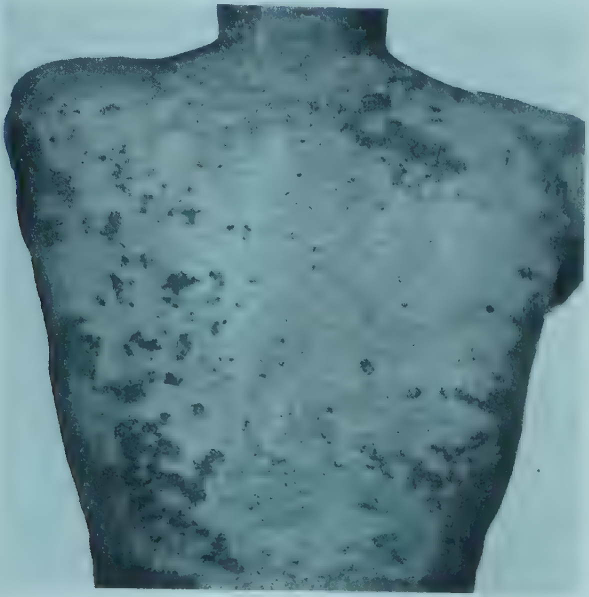

FIG. 70. URTICARIA CAUSED BY ALLERGY TO STRAWBERRIES

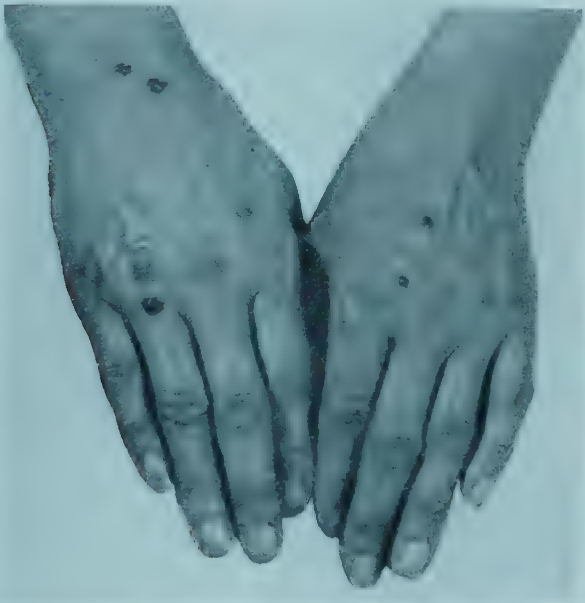

FIG. 71. THROMBOCYTOPENIC PURPURA RESULTING FROM HYPERSENSITIVENESS TO CITRUS FRUITS

Very interesting was the case of a 22 year old patient observed by the writer who, after eating tangerines and oranges, regularly complained of headache and showed a bluish violet discoloration of the face due to vascular dilatation, characteristic of the nitritoid crisis. The appearance of these symptoms was effectively prevented by an injection of adrenalin prior to ingestion of the fruit. Other patients have complained of outbreaks of sweating and of a sensation of heat in the head after eating oranges. Whether it is the protein, the ethereal oil, or the citric acid that is the allergen in a given case of hypersensitiveness to citrus fruit can be determined only by appropriate tests (Urbach and Wiethe[578]). When, for example, Orange Propeptan is beneficial, the protein of the orange may be assumed to represent the allergenic factor; otherwise such methods as outlined on page 236 must be employed.

Behcet described cutaneous manifestations on an allergic basis produced by ingestion of figs or fig preserves.

As a rule, fruit is allergenic only in the raw state; in some cases, however, it is so only when cooked. Occasionally the allergenic action is restricted to certain parts of the fruit (skin, peel, pulp, or seed).

Nuts, particularly peanuts, almonds, Brazil nuts, walnuts, chestnuts, filberts, and pecans, frequently evoke allergies, often severe, usually manifested as urticaria, rhinopathy, or asthma.

Finally, mention should be made here of hypersensitiveness to chocolate (*cocoa*), which is relatively common. Its most frequent clinical symptoms are urticaria, acne, migraine, and allergic rhinitis. On the basis of experimental investigations, Joltrain[602] advanced the opinion that the protein components of the cocoa bean are not nearly so active allergenically as is the cocoa butter. The question can be decided, in a given case, by administering Cocoa Propeptan. When this treatment is beneficial, it shows the cocoa protein to be the causal factor; otherwise, it may be the cocoa fat.

c. Edible Fungi

Among the edible fungi, mushrooms are outstanding as being frequently allergenic. Hypersensitivities to bakers' and brewers' yeast and to the molds used in the manufacture of cheese must be included in this category. Yeast is widely employed in the preparation of raised bread, griddle cakes, fermented beverages such as beer, and some cheeses. It is, of course, also consumed in the form of yeast cakes. Biedermann[613] was able to trace urticaria and angioneurotic edema to the small quantities of yeast in bread and other products. In a case observed by the writer, the patient, an elderly man, had for years been suffering from a wide variety of allergic symptoms (urticaria, migraine, spasm of the urinary bladder, and renal colic) which disappeared as soon as he stopped drinking beer. Here, as

613. BIEDERMANN, J. B.: J. A. M. A. 106: 31, 1936.

well as in another case in which the patient suffered from chronic urticaria, we were able to demonstrate experimentally that the yeast in beer was the causal agent. Occasionally there have been patients with hypersensitiveness to the molds used in the preparation of certain kinds of cheese (Camembert, Roquefort, Gammelost)

d. Spices and Condiments

Spices and condiments act as allergens with relative rarity. Mustard, black pepper, and vanilla seem to be the only items worthy of any serious consideration. Isolated cases have been observed, however, in which there was demonstrable hypersensitiveness to cayenne pepper (paprika), ginger, anise, caraway seed, saffron, nutmeg, peppermint, cloves, poppyseed, cinnamon, and thyme. But in dealing with these substances, one must always bear in mind the possibility of an indirect action due to irritation of the gastrointestinal mucosa. Owing to this irritation, undigested or insufficiently digested proteins of the food may be absorbed and thus enter the blood stream. Figure 72 demonstrates a case showing dermatitis of the face due to cayenne pepper seen by us.

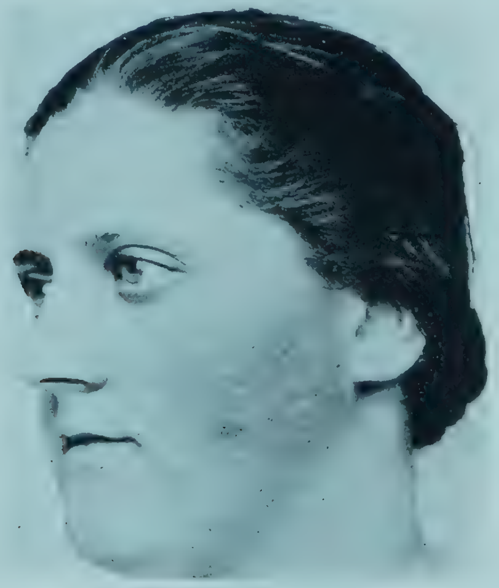

FIG. 72. SUBACUTE DERMATITIS OF THE LEFT CHEEK DUE TO HYPERSENSITIVENESS TO SALT AND TO PAPRIKA

Lesions could be produced at will by giving the patient either salt or paprika by mouth.

e. Gums of Plant Origin

While gum arabic and karaya gum are not really foods, they are often added to prepared foods such as candies, ice creams, gelatin desserts, and diabetic preparations, as well as to emulsified mineral oils and laxatives. They have been observed to elicit urticaria (Bowen[614]), gastrointestinal complaints (Figley[615]), migraine (Alvarez[616]), and other symptoms. Chicle, which is the base of chewing gum, has been reported to produce angioneurotic edema of the larynx (Frank[617]).

f. Beverages

Alcoholic beverages can cause clinical manifestations of allergy both specifically and nonspecifically. Their specific action is due to traces of foreign substances employed in the preparation of the beverage such as barley, malt, and yeast in beer, corn, and rye, or wheat in whiskey; or for the clearing of beverages, such as the use of fish glue, egg white, isinglass, or yeast in cheap white wine. In addition, alcoholic beverages are capable of aggravating allergization nonspecifically by increasing the permeability of the gastrointestinal tract, thus facilitating the absorption of insufficiently digested food proteins in the blood stream. It is well known that in many cases of hypersensitiveness to oysters, for example, the intolerance becomes manifest only when considerable quantities of alcohol are consumed at the same time.

As for the nonalcoholic beverages, milk and cocoa have been discussed above. The great per capita consumption of coffee in this country and the not uncommon occurrences of symptoms attributable to coffee make it necessary to discuss its different pathogenetic actions. First of all, the pharmacologic effect of caffeine has to be considered. Even moderate doses cause vasodilatation which may aggravate dermatoses of vascular origin, such as rosacea, and increase the nervous reactivity of individuals already under tension. The volatile aromatic oils contained in coffee are a gastric irritant (Sollmann[618]) and in susceptible subjects may cause gastrointestinal symptoms. From this pharmacologic action of coffee one must distinguish the allergenic effects. Hypersensitiveness to coffee is not frequently encountered, and in such cases, according to Gutmann[619], one must differentiate between allergy to coffee, to caffeine, and to surrogates added to the coffee. Thus, coffee allergy may be due to products resulting from the roasting process; therefore, in such instances, it is tolerated when the greater part of these substances is removed, as in the specially prepared brands of coffee. However, the appearance of reactions is not prevented by drinking so-called caffeine-free coffee. The latter is, of

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614. Bowen, R.: Arch. Dermat. & Syph. **39:** 506, 1939.
615. Figley, K. D.: J. A. M. A. **114:** 747, 1940.
616. Alvarez, W. C.: J. A. M. A. **114:** 1284, 1940.
617. Frank, D. I.: Arch. Otolaryng. **32:** 1067, 1940.
618. Sollmann, T.: Manual of Pharmacology. Philadelphia: Saunders, 1942. 6th ed.
619. Gutmann, M. J.: Deutsche med. Wchnschr. **59:** 1429, 1933.

course, recommended in cases of hypersensitiveness to caffeine. An interesting case reported by Funck[620] was that of a patient who suddenly reacted with angioneurotic edema and intestinal spasm to a brand of coffee he had been drinking regularly for years in another locality. Painstaking investigation revealed the fact that the water in the town where he had formerly lived had a high calcium content, causing precipitation of the major part of the substances formed during the roasting process and thus rendering them ineffective; the soft water in the locality of his new home merely dissolved these substances.

Hypersensitiveness to coffee may express itself in a great variety of clinical manifestations. Gutmann[619] observed itching, neurodermatitis, urticaria, angioneurotic edema, intestinal spasm, diarrhea, gallbladder colic, rhinopathy, and asthma. Adelsberger and Munter[572] were able to confirm these findings.

Tea is very rarely the cause of allergic conditions. There are isolated reports, however, of hypersensitiveness to herb teas such as camomile or sage tea and others. Bulkley[5] has repeatedly seen nursing infants with severe dermatitides, which had long resisted intelligent and energetic treatment, get well shortly when the mother ceased drinking tea.

3. Vegetable Fats

Vegetable fats may be allergenically active on account of the minute quantities of protein they contain, but they also act in themselves, possibly through their fatty acids. In practice, the question as to which one is the causative factor can be answered by administering Specific Propeptans. If these are beneficial, the hypersensitiveness is shown to be linked with the protein; if not, one may assume the presence of a true hypersensitiveness to fat.

From the allergic standpoint, *cottonseed oil* is by far the most important vegetable fat. It is sold under many trade names, such as Wesson oil, or as salad oil, table oil, or sweet nut oil, as well as under its own generic name. It is widely employed in the manufacture of oleomargarine, Crisco, and Cottolene, and is frequently used as an adulterant in or substitute for olive oil.

Olive oil is frequently adulterated with cottonseed, corn, or other oils. Pure olive oil, however, has been proved to be the cause of at least a few isolated cases of true hypersensitiveness (Vaughan[588]). *Corn oil* is used in salad oils and for shortening in bread and cakes. *Soy bean oil*, which is being used more and more, should be kept in mind as a potential allergen. Finally, nut fats, such as *peanut oil* and *almond oil*, must be mentioned. Hypersensitiveness to cocoa butter has been discussed above.

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620. Funck, C.: Die diätetische Behandlung der Allergie. Leipsig: Barth, 1934.

4. Carbohydrates

Hypersensitiveness to carbohydrates and intolerance of carbohydrates are, of course, two fundamentally different conditions. The former is a rare allergic phenomenon probably based on a hapten mechanism, and the latter is a metabolic disorder generally considered indicative of diabetes mellitus. In either case, administration of sugar is followed by the appearance of cutaneous or general manifestations which disappear after elimination of carbohydrates from the diet. In order to differentiate as to etiology, a sugar tolerance test should be made. This will indicate whether the patient has latent or frank diabetes. If diabetes mellitus is not present in any form, sugar is again given at a time when the patient is free of symptoms, but this is preceded by an adequate injection of insulin. If the manifestations now fail to appear, the case is to be regarded as one of cutaneous carbohydrate intolerance (skin diabetes, see p. 34); if they reappear, as hypersensitiveness to carbohydrates.

We are here concerned only with the latter condition. Both Leiner[621] and Pulay have reported cases of infantile dermatitis in which administration of sugar brought on exacerbations with marked weeping; elimination of sugar resulted in healing of the dermatitis. According to Weigert,[622] hypersensitiveness to carbohydrates is occasionally the underlying cause of strophulus infantum, a claim the present writer has been able to confirm on two occasions. In addition to the two cases of strophulus infantum just mentioned, we made the following observation:

A woman aged 50 presented extensive lichen urticatus refractory to all therapeutic measures (Fig. 73). The glucose tolerance test was normal. Nevertheless, in view of the possibility of retention of carbohydrates in the skin alone (see cutaneous glycohistechia, p. 34), a strict diabetic diet was prescribed, with the result that the condition soon cleared up. Strangely enough, the lesions were exacerbated when insulin was administered together with small quantities of carbohydrate. Close observation for several days revealed that the itching and skin manifestations always recurred when carbohydrates were included in the diet. Since insulin did not bring about tolerance for carbohydrates, the presence of true hypersensitiveness to sugar was assumed. Carbohydrates were almost completely eliminated from the diet for three weeks, and then, as the patient remained free of the symptoms, they were cautiously added in slowly increasing quantities. The skin manifestations did not recur.

In a second case, the patient, a woman of 53, had been suffering for several years from recurrent attacks of an intensely pruritic papular eruption. Trial diets disclosed that ingestion of generous portions of carbohydrate foods brought on marked exacerbation of the pruritus and reappearance of the skin lesions. Elimination of carbohydrates from the diet was promptly followed by definite improvement.

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[621] Leiner, K.: Handb. der Haut u. Geschlechtskr., ed. by J. Jadassohn, vol. xiv, 1930.

[622] Weigert, R.: Monatschr. f. Kinderh. **25:** 669, 1923.

Hypersensitiveness to *honey* should also be mentioned here, a few authenticated cases having been reported. Sometimes the hypersensitiveness relates only to certain types of honey and evidently depends on the source from which the bees have taken it. Thus, cases have been reported of urticarial responses in individuals allergic to buckwheat or to linden, following ingestion of honey from bees that collect pollens from these plants or flowers. It must be remembered, furthermore, that honey frequently contains considerable amounts of pollens which, when taken in large quantities, are capable of eliciting typical symptoms in hay fever patients.

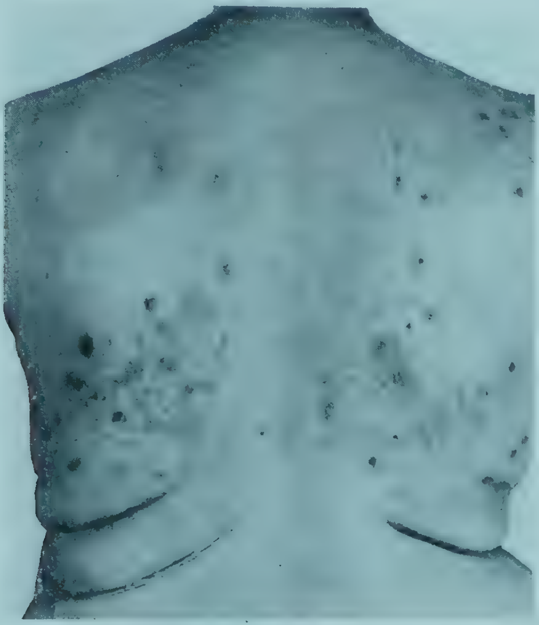

FIG. 73. LICHEN URTICATUS OF MANY YEARS' DURATION ON THE BASIS OF CARBOHYDRATE HYPERSENSITIVENESS

Diagnosis was suggested by severe intensification of itching and recrudescence of the lesions when the patient was placed on a strict elimination diet consisting of sugar and water. The condition was markedly alleviated and later practically cured by means of a diet free of sugar and very low in other carbohydrates.

5. SALTS

Allergic responses to ingested table salt were first reported by Strouse.[623] Vallery-Radot and Rouquès[624] demonstrated the connection between a severe outbreak of urticaria and hypersensitiveness to table salt, based on evidence of positive cutaneous tests with salt, and almost complete disappearance of the urticaria following elimination of table salt from the diet.

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623. STROUSE, S.: Med. Clin. North America 3: 1589, 1920.
624. VALLERY-RADOT, P. and ROUQUÈS, L.: Ann. de dermat. et syph. 10: 1041, 1929.

Gutmann[625] demonstrated that table salt is a relatively frequent cause of such allergic manifestations as urticaria, angioneurotic edema, neurodermatitis, asthma, and migraine.

Urbach and Willheim[577] were the first to undertake a series of investigations along strictly chemical lines intended to ascertain which of the components of the salt was responsible for the hypersensitiveness. These experiments revealed that, in our cases at least, the hypersensitiveness was not in relation to salt (sodium chloride) as such but only to the anion, chloride; the cation, sodium, was tolerated perfectly. These investigations are of importance because they serve to explain why such hypersensitive persons can tolerate salt mixtures that do not contain chlorides as,

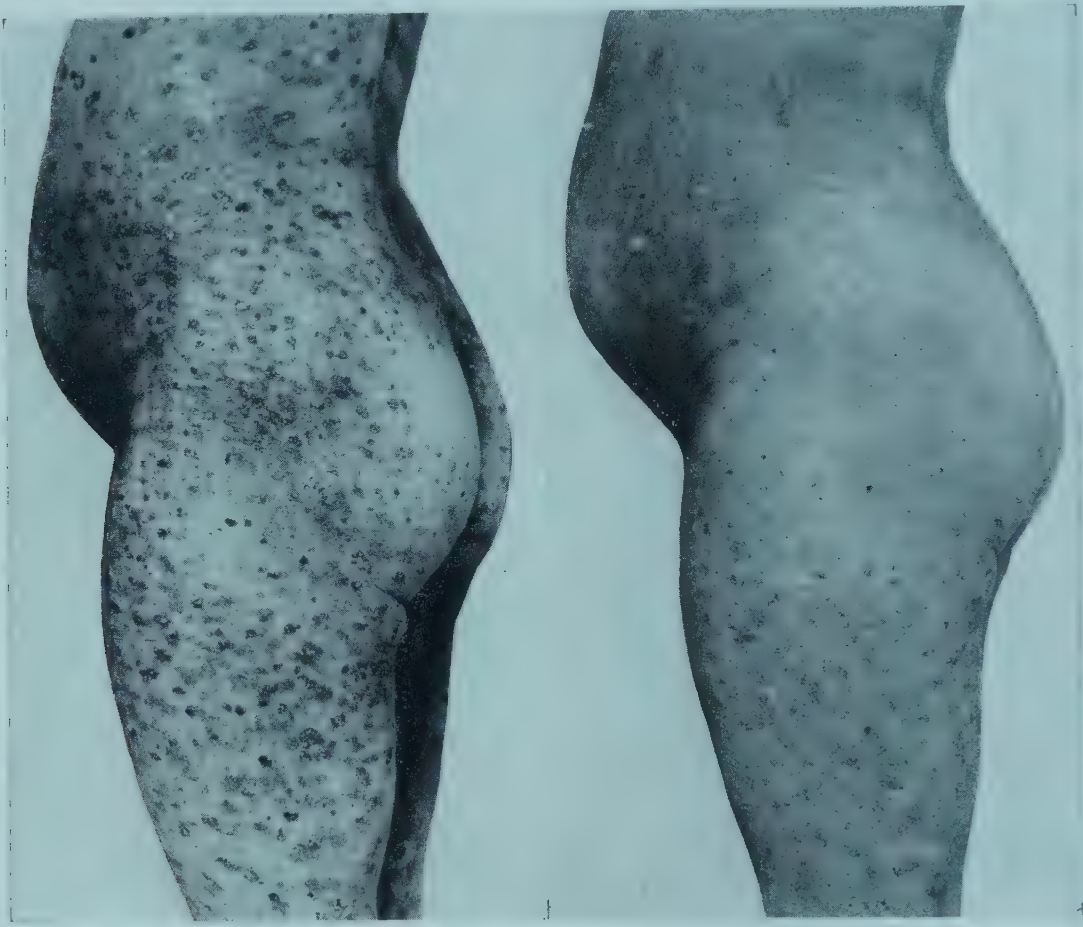

Fig. 74 Fig. 75

Lichen Urticatus of Ten Years' Duration due to Salt, Spices, and Other Foodstuffs

Fig. 74. Appearance of skin lesions before treatment.

Fig. 75. After four weeks of salt-free diet, elimination of spices, and use of Propeptan therapy.

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625. Gutmann, M. J.: Fortschr. d. Therapie **9**: 427, 1933.

for example, Curtasal. Furthermore, the same authors succeeded in demonstrating that anions and cations possess mutually antagonistic properties, thus making it possible to balance the action of the allergic chloride anion by using increased amounts of cations such as sodium citrates, sodium formate, and calcium sulfolactate. Curtasal is an example of such a salt mixture.

The practical significance of hypersensitiveness to salt is illustrated by an example.

Figure 74 shows a prurigo-like dermatosis of about ten years' duration in a woman of 50. The cause of this condition was found to be a hypersensitiveness to protein and to spices which was readily dealt with by means of Propeptan treatment and by elimination of pepper and paprika from the diet. Nevertheless, new eruptions and intense pruritus occasionally reappeared. It was observed that these symptoms regularly occurred after ingestion of highly salted dishes. When the patient was put on a salt-poor diet, these manifestations promptly receded (Fig. 75). They could be made to reappear immediately, however, by administration of 5 Gm. of salt in the form of a powder, or by injection of 600 cc. of physiologic salt solution. Permanent cure (observation period, three years) was achieved by replacing table salt with a chloride-free salt mixture.

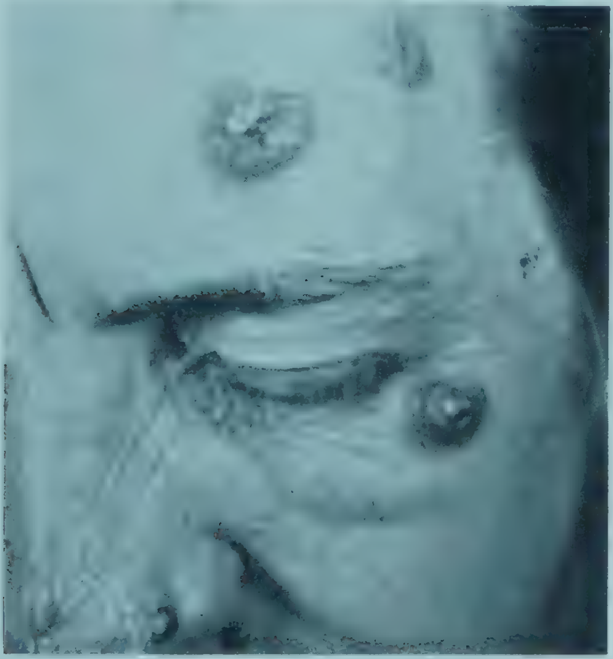

FIG. 76. ERUPTION DUE TO IODINE ALLERGY

This patient was so hypersensitive that the minute amounts of iodine in iodized table salt produced a severe iododerma.

Moncorps[626] reported the case of a middle-aged woman who reacted to ingestion of salt either in the food or as pure table salt with severe episodes of urticaria and angioneurotic edema. However, after removal of a dental granuloma the patient could tolerate salt with impunity.

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[626] MONCORPS, C.: Jahresk. f. ärtzl. Fortbildung 24: 1, 1933.

In occasional instances allergy to table salt is not due to the chloride but to iodine which is added for goiter prophylaxis (Fig. 76).

6. ORGANIC ACIDS

The presence of allergy to certain organic acids and their salts was demonstrated by Willheim and the present writer[577] in a manner similar to that used in the investigation of salt hypersensitiveness. Here, too, the allergic action was restricted to the anions. Naturally, experimental testing must be undertaken in every single case, for we have also observed patients who were allergic to a number of cations. Elimination of the demonstrably harmful substances brings prompt relief.

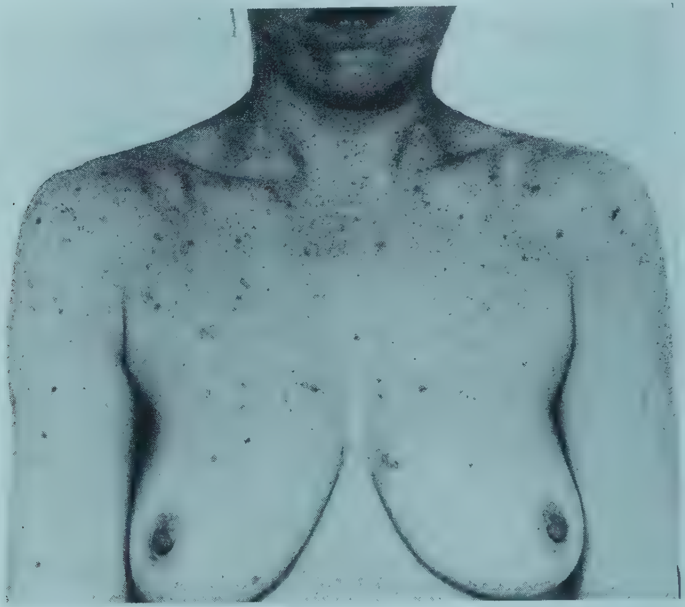

FIG. 77. LICHEN URTICATUS CAUSED BY ACETIC ACID (VINEGAR)

Sour dishes have long been held responsible for the appearance of skin manifestations. Kollert is of the opinion that hypersensitiveness to sour apples, which he observed quite frequently, is attributable to acid. Fuhs[627] reports the case of a woman whose papulo-urticarial exanthem of many years' standing was proved to be provoked by ingestion of sour foods, particularly lemonade. The writer[628] succeeded in demonstrating that an isolated hypersensitiveness to acetic acid (vinegar) was the cause of an urticaria that had been recurring for four years and also of a lichen urticatus (Fig. 77) of one year's standing in a girl of 13. The symptoms in the latter case could also be elicited by oral administration of synthetic acetic acid (100 cc. of a 3 per cent solution), as well as of 0.5 Gm. of acetylsalicylic acid, whereas acetic acid neutralized with sodium bicarbonate was tolerated perfectly. If the possibility of hypersensitiveness to acid is kept in mind, such cases (caused by vinegar, wine, oranges, lemons, pickles, and similar foods) will be found much more often than the literature would lead one to suppose.

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[627] FUHS, H.: Zentralbl. f. Haut- u. Geschlechtskr. **32:** 35, 1930.

[628] URBACH, E.: Zentralbl. f. Haut- u. Geschlechtskr. **44:** 502, 1933.

7. Food Odors

The possibility that a presenting dermatosis may be directly due to some food odor is likely to be overlooked. Needless to say, food odors are not ingestants, but inhalants. They act as excitants only in patients who are so highly hypersensitive to animal or vegetable protein that the mere effluvium of a specific food suffices to elicit cutaneous symptoms identical with those following actual ingestion of the foods in question. Sutton,[603a] Dekker,[552] Kaemmerer,[595] Lewis and Grant,[596] Boss,[597] Horesh[630] and the present writer[631] have noted strong reactions (urticaria, angioneurotic edema, dermatitis, infantile dermatitis, and even general anaphylactic symptoms) in individuals allergic to egg, fish, meat, cabbage, onion, garlic, or the like when they were merely present in a room where an egg was being opened, or where fish, meat, or the vegetables mentioned were cooked. Unless this possibility is kept in mind, some patients will continue to suffer from foods they never eat.

C. DIAGNOSIS OF FOOD ALLERGY

For the identification of allergenic foods four methods are at our disposal: skin tests, trial tests, elimination diets, and Propeptan diet. In addition, the accelerated pulse rate (Coca[632]) and the leukopenic index (Vaughan[588]) may be used.

1. Skin Tests

In the opinion of the present author, the all too common failure to diagnose and treat properly a presenting skin condition as an expression of food allergy, despite strong indications to that effect in the patient's history, is chiefly attributable to the fact that cutaneous and intracutaneous tests are still being widely used as the principal method of identifying the nutritional allergen. The writer feels that if conclusions are drawn from these tests alone the entire approach must be described as not only worthless but downright misleading. A skin test is significant only when correlated with the clinical history and with the outcome of appropriate oral tests, such as elimination and oral exposure tests. This opinion is shared by Alvarez,[633] Rowe,[634] Rackemann,[635] and many others. Alvarez[591] is most outspoken: "It is unfortunate that so many patients get the idea that the skin tests are like gospel truth." In studies on a large group of patients, Rinkel[636] found that only about 20 per cent of the foods actually responsible for the allergic symptoms will elicit skin reactions.

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[630] Horesh, A. J.: J. Allergy **14:** 335, 1943.

[631] Urbach, E.: J. Allergy **13:** 387, 1942.

[632] Coca, A. F.: Non-reagenic Familial Food Allergy. Springfield, Ill.: Thomas, 1943.

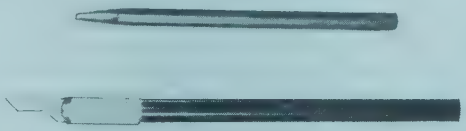
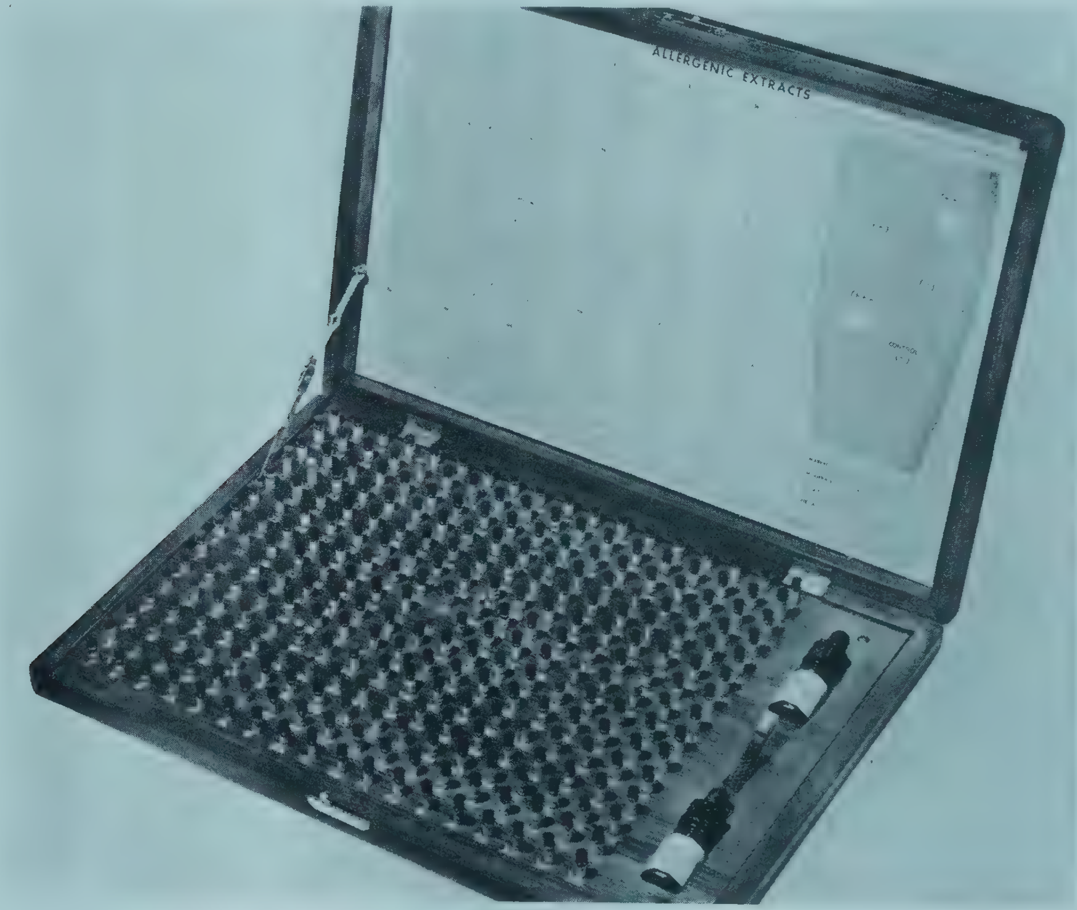


FIG. 78. INSTRUMENTS FOR SCRATCH TESTING

a. Borer useful in testing small children.
b. Small knife.



(Courtesy of E. R. Squibb and Sons.)

FIG. 79. DIAGNOSTIC OUTFIT FOR SCRATCH TESTING

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633. ALVAREZ, W. C.: Minnesota Med. **22:** 92, 1939.
634. ROWE, A. H.: J. Allergy **5:** 135, 1934.
635. RACKEMANN, F. M.: Clinical Allergy. New York: Macmillan, 1931.
636. RINKEL, H. J.: Ann. Allergy **2:** 115, 1944.

If skin tests are to be made, the writer prefers the cutaneous (Figs. 78, 79) to the intracutaneous method, because the reactions to the former are more specific and also less dangerous. However, the Wyeth Tubex Outfit for intracutaneous testing, using only 0.01 to 0.02 cc. of the allergen, is a convenient, specific and rather safe method, as determined by O. Belmont in the Allergy Department of the present writer.

It may be helpful to present briefly the causes leading to positive and negative cutaneous and intracutaneous tests, especially in regard to their specificity and usefulness in identifying the causal agents in a given case of food allergy.

In testing with various proteins, one often encounters positive reactions which must be regarded as nonspecific, since elimination from the diet of the substances eliciting positive responses does not bring about clinical improvement. This may be due to many different causes. For example, cutaneous reactions may be demonstrable for many years after the allergic symptoms have subsided and would merely indicate a former sensitization of the skin to a given food. Or the positive skin test may be the evidence of exposure and latent sensitization which is not the cause of the presenting skin disease. Particularly interesting, in this connection, are the commonly encountered cases of infantile dermatitis which give positive responses to egg white, but which do not show clinical improvement when egg is eliminated from the diet (see p. 381). Moreover, a false positive reaction may be due to a nonspecific hyperreactivity of the capillary system. This state may be suspected when a patient's skin reacts to all extracts, including controls (Fig. 80), instead of responding only to some of the extracts and not at all to the control injections (Fig. 81). On the other hand, there are many individuals with food allergy, notably those having manifestations

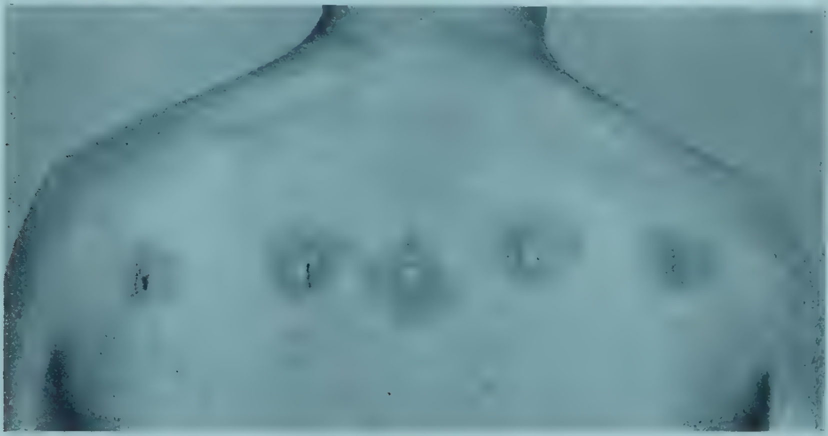

FIG. 80. POSITIVE INTRACUTANEOUS TESTS WITHOUT DIAGNOSTIC SIGNIFICANCE

If all or most of the skin sites respond to various allergens, reactions must be considered nonspecific and are of no aid in establishing etiologic diagnosis. In this subject, even saline control (at left) produced small wheal.

in the form of urticaria, lichen urticatus, and prurigo mitis, who fail to react to cutaneous tests but who respond with an allergic dermatosis (e.g., shower of urticarial wheals) when tested orally with the particular protein.

A negative skin test in a patient presenting characteristic allergic reactions to the same substance taken by mouth may be explained in a number of ways. For one thing, the allergy may have been caused not by the food protein itself, but by metabolic products or derivatives of the protein formed in the intestine (Alvarez and Hinshaw[637]) and thus acting as a secondary allergen (Urbach[26]). Hopkins and Kesten[638] have shown that there are cases in which intracutaneous tests with extracts of whole egg or wheat flour elicit no reactions, while the various protein constituents of these foods (ovomucin, albumin, globulin, gliadin, glutenin), injected separately, evoke positive cutaneous responses in conformity with the patient's generalized hypersensitiveness. The lability of the antigen in fruit juices probably accounts for the frequent failure to obtain positive cutaneous reactions with the usual stock fruit extracts in clinically sensitive patients. Thus, Tuft and Blumstein,[611] confirmed by Cooke,[612] found that freshly extracted fruit juices elicited positive reactions in a high percentage of cases, while standard concentrated liquid and powdered extracts generally evoked no response whatsoever.

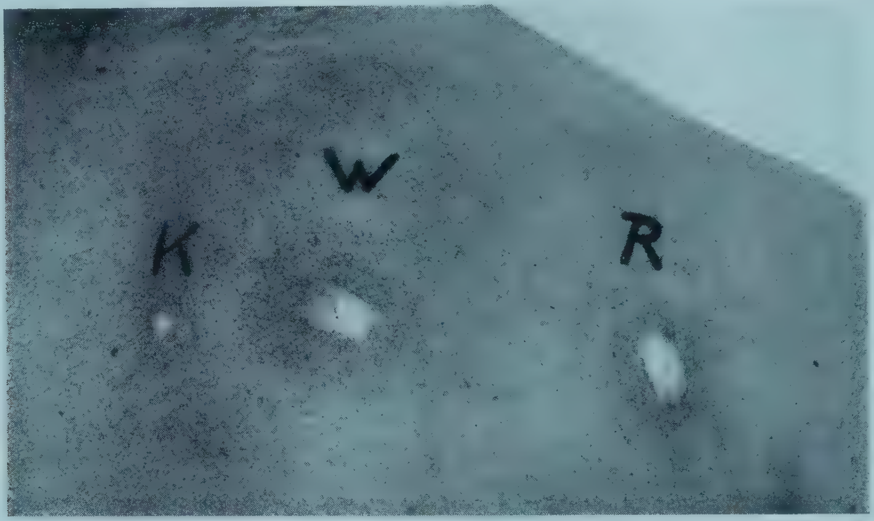

FIG. 81. INTRACUTANEOUS TESTS OF DIAGNOSTIC SIGNIFICANCE
Reading left to right: control negative, wheat positive, and rye positive.

Another and more technical reason why it is extremely difficult, not to say impracticable, to perform truly accurate intracutaneous tests in cases of high-grade hypersensitiveness, is that it is imperative to have separate

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637. ALVAREZ, W. C. and HINSHAW, H. C.: J. A. M. A. **104:** 2053, 1935.
638. HOPKINS, G. and KESTEN, B.: Delib. 8th Internat. Dermat. Congress **8:** 602, 1930.

syringes and needles available for each allergen. Furthermore, it is necessary to prepare fresh extracts approximately every three months, since they tend to lose their specificity after a while. However, these precautions are unnecessary when one employs the scratch technic in which dried powdered allergens are used.

There is still another reason why we disapprove of the intracutaneous method of testing for general use, and feel that it should be resorted to only in special allergy clinics or by experienced specialists—namely, the danger involved. In cases of high-grade hypersensitiveness, such injections frequently elicit systemic reactions which sometimes assume the proportions of severe anaphylactic shock. Thus, Kaemmerer[595] has described a catastrophic reaction of this sort following a test injection of fish extract; and Lehner[639] observed a similar response to a test with milk. The importance of severe delayed reactions was brought out by Cooke,[587] who reported four cases in which severe systemic manifestations made their appearance from three to six hours after performance of negative intracutaneous tests. The present writer is in a position to confirm this most important observation, notably in regard to tests with egg. A few instances of even fatal anaphylactic reactions are to be found in the literature. Baagö[640] has reported a case of fatal shock following intracutaneous injection of 0.1 cc. of egg protein, and Cooke[641] described a case in which death followed the introduction of 0.03 cc. of fish glue extract intracutaneously.

If, for reasons mentioned, we are definitely opposed to the general use of the intracutaneous method, there is one cutaneous test which may be recommended because it has the double advantage of being highly specific and in no way dangerous. This is the passive transfer method, also known as the Prausnitz-Kustner test, by means of which it can be determined whether the patient is specifically hypersensitive to a given substance. In cases in which the extremely high degree of the allergy makes it dangerous to undertake a direct cutaneous test or one by the oral route, or in which the children's parents refuse to permit the performance of skin tests, as well as in cases in which the consistency of the skin is abnormal (as in ichthyosis or urticaria, for example) or in which the cutaneous reaction is likely to be pathologic (e.g., severe dermographism), the passive transfer method is recommended. The technic is as follows: 0.1 cc. of the patient's blood serum is injected intracutaneously into a duly tested, nonhypersensitive control individual. Twenty-four hours later the food in question is administered to the control person,

639. Lehner, E.: in Lehner, E. and Rajka, E.: Allergie erscheinungen der Haut. Halle: Marhold, 1927.
640. Baagö, K. H.: Zentralbl. f. Haut- u. Geschlechtskr. **30:** 709, 1929.
641. Cooke, R. A.: J. Immunol. **7:** 219, 1922.

either by injection at the site where the patient's blood serum was given or, as suggested by M. Walzer,[561] by mouth. If the sensitized skin area reacts with a wheal, it means that the patient is hypersensitive to the food with which the test was made. Walzer's modification is especially clear-cut and convincing. With the aid of this so-called "indirect method," Peshkin and Fineman[642] have obtained positive reactions in no less than 23 per cent of their cases thus tested.

2. Trial Diet

When the history or the clinical course of the allergic disease tends to direct suspicion to a food, the so-called trial diet or food addition method can serve to identify the responsible agent. In this procedure the results of controlled administration of foods are observed.

In order to prescribe a diet which is for all practical purposes allergen-free and at the same time provides for the basic caloric needs of the patient, we allow our own cases only sugar and water at the start. This would be contraindicated solely in the exceedingly rare cases of allergy to carbohydrates.

The test is carried out at home, on a daily intake of 300 to 400 Gm. (10 to 13 ounces) of sugar dissolved in water, for two days. If the skin or mucous membrane manifestations disappear within this period, the patient is given one new food each day, simply prepared and not mixed with any other nutrient. In order to arrive at an adequate diet as soon as possible, it is best to begin with foods that rarely have an allergic effect. For example, the first day's diet may well consist of boiled rice; on the second day, potatoes in jacket; third day, apples; fourth day, lamb; fifth day, carrots; sixth day, chicken; and so on. If one of these added foods is followed by an attack of urticaria, dermatitis, or other allergic manifestations the suspected item is omitted from the diet. After the allergic symptoms have subsided, this food is again given in order to ascertain whether it will repeat the reaction. If the symptoms then do appear, one nutritive allergen seems definitely to have been found. However, the oral testing must be continued with all the foods commonly included in the patient's diet, since there are usually several foods responsible in such cases. When neither animal nor vegetable proteins elicit responses, tests must be made with carbohydrates other than table sugar and with fats, salts, acids, spices, and volatile oils (consumed, for example, in citrus fruits, flavored candies, chewing gums, and the like).

According to the patient's age and the particular environmental circumstances, the physician's suspicion may be directed toward certain foods. For instance, tests must sometimes be performed not only with cow's milk, but also with human and goat milk. Furthermore, as has been mentioned elsewhere (p. 213), the manner in which a given food has been prepared must frequently receive special attention (raw versus cooked eggs or fruit). The quantity consumed may also play an important role. For example, an individual may be able to tolerate a small quantity of milk but may react allergically to a greater amount. The feeding tests should therefore be performed with about the same quantities of the various foods as are normally eaten by the patient.

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[642] Peshkin, M. M. and Fineman, A. H.: Am. J. Dis. Child. 37: 39, 1929.

The writer observed the case of a young man who had urticaria after taking 750 cc. (1½ pints) of milk, while 10 cc. (⅓ oz.) of milk evoked no reaction. This seems to contradict the original concept of hypersensitiveness, according to which only the quality and not the quantity of the allergen was significant. Some cases of even a high degree of hypersensitiveness give evidence of being influenced by the quantitative factor. And of course the very principle of hyposensitization is based upon such dilutions of the allergen as will stimulate antibody production without eliciting allergic manifestations. In recognition of this quantitative factor, it is therefore appropriate, in given cases, to undertake quantitative tolerance tests with increasing amounts of the nutritive allergen.

When the physician has good reason to suspect a certain food (e.g., milk or eggs), the test with this substance should be postponed until near the end of the series, by which time the patient will be on a sufficiently nourishing and varied diet, consisting of foods proved to be tolerated.

The trial diet is thus a test that can be performed easily enough in almost any ambulatory case. If the patient keeps a careful record of all foods eaten as well as of any general or local manifestations that may appear, this will materially help the physician.

The trial diet may, however, be refused by many patients, especially those who do strenuous work, and by the mothers of feeble children, because it produces a sense of hunger and some degree of undernutrition.

3. Elimination Diets

Elimination diets constitute another method for detecting nutritional allergies. These diets are designed to exclude those foods which most commonly act as allergens. The best known and most widely used diets of this kind are those devised by Rowe,[643] whose recent and very valuable monograph on the subject presents a clear and comprehensive outline of the technic, as well as a number of detailed recipes and menus for each type of elimination diet. As outlined in Table 49, Rowe suggests four different dietaries, of which one consists of milk alone. In the others, it will be noted that no food item is contained in more than one diet; furthermore,

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[643] Rowe, A. H.: Elimination Diets and the Patient's Allergies. Philadelphia: Lea and Febiger, 1944.

TABLE 49.—*Elimination Diets* (*Rowe*[643])
(*Second Revision*)

Diet 1	Diet 2	Diet 3	Diet 4
Rice Tapioca	Rye	Tapioca White potato	Milk† Tapioca
Rice biscuit Rice bread	Corn pone Corn-rye muffin Rye bread Ry-Krisp	Breads made of any combination of soy, Lima, and potato starch and tapioca flours	Cane sugar
Lettuce Chard Spinach Carrot Sweet potato or yam	Beets Squash Asparagus Artichoke	Tomato Carrot Lima beans String beans Peas	
Lamb	Chicken (no hens) Bacon	Beef Bacon	
Lemon Grapefruit Pears	Pineapple Peach Apricot Prune	Lemon Grapefruit Peach Apricot	
Cane sugar Sesame oil Olive oil* Salt Gelatin, plain or flavored with lime or lemon Maple syrup or syrup made with cane sugar flavored with maple Royal baking powder Baking soda Cream of tartar Vanilla extract Lemon extract	Cane or beet sugar Mazola oil Sesame oil Salt Gelatin, plain or flavored with pineapple Karo corn syrup White vinegar Royal baking powder Baking soda Cream of tartar Vanilla extract	Cane sugar Sesame oil Soy bean oil Gelatin, plain or flavored with lime or lemon Salt Maple syrup or syrup made from cane sugar flavored with maple Royal baking powder Baking soda Cream of tartar Vanilla extract Lemon extract	

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* Allergy to olive oil may occur with or without allergy to olive pollen. Mazola oil may be used if corn allergy is not present.

† Milk should be taken in quantities up to two or three quarts a day. Plain cottage cheese and cream may be used. Tapioca cooked with milk and cane sugar may be taken.

none of these three dietaries includes wheat, milk, or eggs, which are properly regarded as the most frequent offenders. The physician prescribes that dietary which does not contain the foods that have aroused suspicion, on either the basis of a history of intolerance or aversion, of actual distress after eating, or on the strength of skin tests. If the patient's history provides no clue as to which foods may be offenders, but is reasonably sure that milk does not disagree with him, Diet 4 is prescribed. These dietaries are to be maintained for ten days. It should be borne in mind that the patient must receive adequate nourishment throughout this period. Thus, when eggs and milk products are excluded, the patient must be given generous quantities of the meat specified in the diet twice daily, in order to maintain an adequate protein intake. Legumes add considerably to a diet's protein content, and proteins are especially desirable because they contain most of the amino acids essential to protein synthesis in the human organism. When milk is excluded for some time, children should be given dicalcium phosphate, 4 to 6 Gm. (60 to 90 grains) daily, and adults calcium carbonate, 2 to 3 Gm. (30 to 45 grains) daily, in order to maintain the mineral balance. Furthermore, the patient requires an adequate supply of vitamins. If the patient is deficient in vitamin A, he is to receive Caritol or Carotene (8 to 10 drops), preferably in sesame oil or in corn oil, provided corn is permitted in the diet. Thiamine hydrochloride, 10 mg., and vitamin B complex, 2 capsules, may be given if the diet is low in these vitamins. Ascorbic acid 50 mg. is to be prescribed in cases of allergy to citrus fruits. The regular elimination diets are deficient in vitamin D. If exposure to the sun is not feasible a preparation free of fish oil, such as Viosterol or Drisdol (10 drops), should be taken by the patient.

It is often possible to discover, by means of the elimination diets, the identity of allergenic foods. But the elimination diet method has several definite disadvantages. In the first place, each diet must be maintained for from seven to ten days; second, in practice it is not ordinarily feasible to prepare a diet totally excluding the foods most commonly consumed, even if only because of financial considerations; third—and this is a most important drawback—if any of the first three diets is not tolerated, one cannot know which of its twenty or so constituent foods are the causative agents.

Since the physician is often asked precisely which foods may be eaten and which must be omitted in a milk-, egg-, or wheat-free diet, as well as in one which excludes all three items, we reproduce the tables compiled by Ralston Purina Company, St. Louis, Mo. (Tables 50–53).

At this point we should like to second Alvarez' demand[644] that federal statutes be enacted requiring that all the constituents of processed foods be

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[644] ALVAREZ, W. C.: Am. J. Digest. Dis. 5: 801, 1939.

Table 50.—*Egg-free Diet*

The following foods are prohibited:

Baking Powder
Any that contains egg white or albumen. Read the labels.

Beverages
Coffee, if egg white or shells have been used to clarify it. Root beer which may have had egg added to make it foam. Any prepared drink made with eggs or from powders containing egg, egg powders, dried egg or albumen.

Breaded Foods
If the breading mixture used contains egg or crumbs that contain egg.

Breads
Muffins, griddle cakes, waffles, gingerbreads, doughnuts and fancy breads, such as nut, fruit, etc. Commercial breads and rolls that have egg as an ingredient or that have been brushed with egg white to glaze the top. Any homemade bread containing egg. Prepared mixes for pancakes, waffles, biscuits, muffins, doughnuts, breads and rolls unless the list of ingredients on the label shows no egg, egg powders, dried egg or albumen.

Desserts
Bavarian creams. Stirred or soft and baked custards. Doughnuts, fritters, angel and sponge cakes, macaroons, meringues and whips. Pie fillings containing eggs, such as custard, lemon, coconut cream and pumpkin. Blanc manges, frostings, puddings, cakes, cookies ice creams and sherbets unless made at home without eggs or from prepared mixture that does not contain egg, egg powders, dried egg or albumen.

Egg Dishes
Baked, coddled, creamed, deviled, scalloped, fried, poached, scrambled, shirred, hard or soft cooked eggs, egg drinks, egg sauces, egg meringues, souffles and omelets. Do not use dried or frozen eggs. Do not use any mixture that contains eggs, egg powders, dried eggs or albumen.

Meats, Poultry, Game, Fish and Seafood
Sausages, loaves, croquettes or any meats using egg as a binding agent.

Miscellaneous
French toast, fritters and timbales. Any prepared mix unless label shows it contains no egg, egg powders, dried egg or albumen.

Salad Dressings
All salad dressings except true French dressing unless homemade without eggs or unless the list of ingredients on the label shows no egg, egg powders, dried egg or albumen.

Sauces
Hollandaise, tartar and egg.

Soups
Mock turtle, alphabet and egg noodle soups. Consommes, bouillons, broths, or any soup cleared with egg or containing ingredients made with egg. Carefully read labels of dehydrated and canned soups and do not use if they contain egg, egg powders, dried eggs or albumen.

Sweets
Divinities. Any homemade candy containing egg. Read the list of ingredients on the label of all wrapped candies and do not use if they contain egg, egg powders, dried egg or albumen. (Caution: Many commercial candies made without eggs are brushed with egg white to give them lustre.)

The following foods are permitted:

Beverages
All plain milks. Cocoa, tea and coffee (unless cleared with egg or egg shells). Fresh, frozen and canned fruit juices. Mineral and carbonated waters.

Breads
Ry-Krisp, corn pone, plain and beaten biscuits, and plain crackers. Any homemade breads made from egg-free recipes. Many commercial breads and rolls have eggs, dried eggs or egg powders as an ingredient, or are brushed with egg white to glaze the top.

Desserts
Plain, fruit-flavored and fruit gelatins. Eggless blanc manges. Plain junkets. Fruit pies. Ices and mousses. Cookies, frostings, cakes, puddings, dumplings, ice creams and sherbets made at home without eggs. Read labels on *all* prepared mixes for they often contain egg, dried egg, egg powders or albumen.

Fats and Salad Dressings
Butters and margarines. Meat, poultry and vegetable fats and oils. Eggless French dressing and eggless mayonnaise. Read the label carefully on commercial French dressing for it may contain egg, egg powders, dried egg or albumen.

Miscellaneous
Popcorn, nuts, olives, pickles, chili powders, condiments, flavoring extracts, herbs, salt, spices. Plain dumplings, macaroni and spaghetti and eggless noodles.

Sauces and Gravies
Cream, white, tomato, meat, vegetable and chili sauces. Gravies. Catsups.

Soups
Cream, meat, fish and vegetable soups prepared without eggs or ingredients containing eggs: (such as egg noodles).

Table 50—*Continued*

Breaded Foods
If egg or bread crumbs containing eggs are not used in the breading mixture. *Evaporated milk can be used in place of egg; Ry-Krisp crumbs in place of bread crumbs.*

Cereals
Any desired breakfast cereal. Barley, cornmeal, hominy, rice and tapioca prepared without eggs.

Fruits
Fresh, frozen, dried, canned—raw or cooked without eggs.

Meats, Poultry, Game, Fish and Seafood
Prepared without eggs.

Meat Alternates
Dried peas, beans, lentils, cheeses, nuts, peanut butter. Use no eggs in preparation.

Milk and Milk Products
Fresh, whole and skim milk. Evaporated, condensed, dried, malted, cultured and buttermilk. Butters, cheeses and creams.

Sugars and Sweets
Brown, granulated, powdered and confectioner's sugars. Honey, molasses, sorghum and syrups. Jellies, jams, marmalades and preserves. Hard candies and homemade egg-free candies. Wrapped commercial candies that contain no egg, egg powders, dried egg or albumen in the list of ingredients.

Vegetables
Fresh, frozen, dried, canned—raw or cooked. Do not combine with eggs.

Table 51.—*Milk-free Diet*

The following foods are prohibited:

Beverages
Made with milk or with chocolate, cocoa or preparations containing milk or milk products.

Breads
Doughnuts, popovers, pancakes, waffles, rusks and crackers, except Ry-Krisp. Wheat, rice, rye, corn, graham, gluten, soybean breads and rolls—made with milk or milk products. *Most commercial breads and rolls contain milk or milk products.*

Breaded Foods
If the breading mixture contains milk or crumbs from breads and crackers containing milk or milk products.

Desserts
Cakes, cookies, puddings, and pie crusts made or brushed with milk or milk products. Bavarian creams, blanc manges, custards, junkets, ice creams, mousses and milk sherbets. Prepared mixes containing milk or milk products.

Fats and Salad Dressings
Butters and margarines. Salad dressings containing milk, cream, butter, margarine or cheese.

Meats, Poultry, Game, Fish and Seafood
Dishes prepared with milk or milk products. *Commercially prepared meats frequently contain milk or milk products.*

Milk and Milk Products
Fresh, whole and skim milks. Cultured and buttermilk. Creams. Condensed, evaporated, dried milk and milk solids. Casein and lactalbumin. Butters and margarines. Curds and wheys. Powdered and malted milks. All cheeses.

Miscellaneous
Creamed and scalloped foods. Foods dipped in milk batter or fried in butter or margarine. Foods prepared au gratin (with cheese). Rarebits and timbales. Prepared mixes for biscuits, cakes, cookies, doughnuts, muffins, pie crusts and waffles if they contain milk or milk products.

Sauces and Gravies
White, cream, butter and hard sauces or any sauce or gravy made with milk or milk products. Any food using a white or cream sauce in its preparation.

Soups
Canned and dehydrated soups containing milk or milk products or any soup made with milk or milk products.

Sweets
Made with milk or milk products.

Vegetables
Creamed and scalloped vegetables and those prepared and served in any way with milk or milk products.

Milk and Milk Products—Fresh, whole and skim milks. Cultured and buttermilk. Cream. Condensed, evaporated, dried milks and milk solids. Casein and lactalbumin. Butters and margarines. Curds and wheys. Powdered and malted milks. All cheeses.

TABLE 51—*Continued*

The following foods are permitted:

BEVERAGES
Made with water and milk-free chocolate or cocoa. Coffee and tea served without milk or cream. Fresh, frozen and canned fruit juices. Mineral and carbonated waters.

BREADS
Ry-Krisp. Wheat, rice, rye, corn, graham, gluten and soybean bread and rolls made at home without milk or milk products.

BREADED FOODS
If milk or crumbs from breads and crackers containing milk or milk products are not used in the breading mixture. *Ry-Krisp can be used.*

CEREALS
All ready-to-eat and cooked cereals served without milk or cream. *Fruit sauces can be served on cereal or dried fruits can be added to a thin cooked cereal.*

DESSERTS
Plain and fruit-flavored gelatins. Angel and sponge cakes. Cakes, puddings, shortcakes, cookies and pie crusts made at home without milk or milk products. Fruit ices made with water. Meringues.

EGGS
Soft and hard-cooked, poached and coddled. Omelets, souffles (see recipes), scrambled and fried eggs if shortening replaces butter or margarine and water or vegetable liquid replaces milk. Deviled eggs made without milk or milk products.

FATS AND SALAD DRESSINGS
Poultry, meat and vegetable fats and oils. French dressing, mayonnaise and other salad dressings made without milk or milk products.

FRUITS
Fresh, frozen, dried, canned—raw or cooked—served without milk or milk products. Can be sweetened with sugar, honey, molasses or sirups.

MEATS, POULTRY, GAME, FISH AND SEAFOOD
Prepared without milk or milk products. (Caution: some commercially prepared meats such as frankfurters, hamburgers, meat loaf and sausages frequently contain milk or milk products.)

MEAT ALTERNATES
Eggs, nuts, peanut butter, dried peas, beans and lentils prepared without milk or milk products.

MISCELLANEOUS
Flavoring extracts, nuts, olives, pickles, herbs, chili powders, condiments, salt and spices. Popcorn prepared without butter or margarine.

SAUCES AND GRAVIES
Catsups. Gravies, meat and other sauces made without milk or milk products.

SOUPS
Made at home without milk or milk products. Bisques and chowders made with water.

SUGARS AND SWEETS
Brown, granulated, powdered and confectioner's sugars. Honey, molasses, sorghum and syrups. Jellies, jams, marmalades, and preserves. Hard candies. Candies made at home without milk or milk products. Wrapped commercial candies containing no milk or milk products in the list of ingredients.

VEGETABLES
Fresh, frozen, dried, canned—raw or cooked—prepared and served without milk or milk product

TABLE 52.—*Wheat-free Diet*

The following foods are prohibited:

BEVERAGES
Coffee substitutes and other beverages made from wheat products. (Check labels for ingredients.) Malted drinks, beer and ale.

BREADS
Whole wheat, graham, gluten and white breads, rolls, muffins and, biscuits. Doughnuts, popovers, sweet-rolls, johnny cake, pancakes, waffles, rusks, pretzels, zwieback and crackers (except Ry-Krisp). Prepared mixes for pancakes, waffles, biscuits, muffins, doughnuts, breads and rolls. Rice, potato and soybean breads, rolls, muffins, and biscuits; corn and rye breads, rolls and muffins unless made at home without wheat flour.

DESSERTS
Cakes, doughnuts, dumplings, pastries, commercial sherbets, ice creams and ice cream cones. Custards, cookies, pies and puddings made with wheat products. Prepared mixes for cakes, cookies, ice creams, puddings and pie crusts, unless the list of ingredients on the label shows no wheat products.

MEATS, POULTRY, GAME, FISH AND SEAFOOD
Swiss steak. Bread and cracker stuffings. Chili con carne, croquettes, fish or meat patties and loaves, unless made at home without wheat products. Commercially and dealer-prepared meats frequently contain wheat products.

SALAD DRESSINGS
Any salad dressing thickened with wheat flour.

SAUCES AND GRAVIES
Gravies, butter sauces, cream and white sauces unless homemade without wheat flour. Read labels on commercial sauces and do not use if they contain wheat products.

SOUPS
Cream, unless made at home without wheat flour. Vegetable and meat soups, chowders and bisques if thickened with wheat products.

SWEETS
Commercial candies that contain wheat products. Read labels.

Table 52—*Continued*

Breaded Foods
In which breading mixture contains wheat products.

Cereals
Wheat cereals and those containing wheat or wheat products. (Read labels carefully.)

Miscellaneous
Malt products. Dumplings, noodles, spaghetti, macaroni, ravioli, mostaccioli, vermicelli, soup rings, alphabets and kindred products.

Vegetables
Any vegetable prepared or served with a sauce thickened with wheat flour or those prepered and served in any way with wheat products.

Wheat and Wheat Products include: (1) all the following flours: white, bread, all-purpose, cake, pastry, self-rising, wheat, whole wheat, entire wheat, cracked wheat, graham, enriched: durum, phosphated; (2) also: wheat, wheat germ, bran, farina, semolina; (3) and in addition, cracker meal, bread crumbs and malt.

The following foods are permitted:

Beverages
Chocolate, cocoa, coffee and tea. Fresh, frozen and canned fruit juices. Mineral and carbonated waters.

Breads
Ry-Krisp. Corn pone, southern spoon bread and other homemade corn and rye breads made without wheat flour.

Breaded Foods
Prepared without wheat products. *Ry-Krisp crumbs can be used.*

Cereals
All ready-to-eat and cooked cereals except those made from or containing wheat or wheat products.

Desserts
Bavarian creams, cornstarch puddings, soft or stirred and baked custards, ices, mousses, meringues, tapioca and rice puddings, Indian puddings, junkets and gelatins. Ry-Krisp crumb crust. Homemade ice creams, sherbets. Oatmeal, rice and rye cookies made without wheat products.

Eggs
Coddled, fried, hard and soft-cooked, poached, scrambled. Omelets. Souffles made without wheat products.

Fats and Salad Dressings
Butters, margarines, animal and vegetable fats and oils. French dressing and mayonnaise. Other homemade salad dressings prepared without wheat flour.

Fruits
Fresh, frozen, dried, canned—raw and cooked—prepared and served without wheat products.

Meats, Poultry, Game, Fish and Seafood
Prepared without wheat products. *Ry-Krisp stuffing can be used.* (Caution: Some canned and commercially prepared meats, such as frankfurters, "cold cuts," sausages and some dealer-prepared meat patties frequently contain wheat products.)

Meat Alternates
Dried peas, beans, lentils, cheese, nuts, peanut butter and eggs prepared without wheat products.

Milk and Milk Products
Fresh, whole and skim milks. Cultured and buttermilk. Condensed, evaporated and dried milks. Butter, cheeses and creams.

Miscellaneous
Chili powders, condiments, flavoring extracts, herbs, nuts, olives, pickles, popcorn, salt and spices.

Sauces and Gravies
Bottled sauces containing no wheat products (read labels). Homemade sauces and gravies prepared without wheat flour.

Soups
Clear bouillions and consommes. Other soups made at home without wheat products. *Rice, barley and Ry-Krisp crumbs can be used for thickening.*

Sugars and Sweets
Brown, granulated, powdered, confectioner's and maple sugars. Honey, molasses, sorghum and syrups. Jellies, jams, preserves and marmalades. Candies made without wheat products. (Caution: Many commercial candies contain wheat products. Read the labels.)

Vegetables
Fresh, frozen, dried, canned—raw and cooked. Do not combine with wheat products. Butter, margarine, drippings, milk, cream, cheese, or eggs can be used in preparation.

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accurately listed on the label of their containers. Moreover, changes in composition, such as partial substitution of corn or soy bean flour for wheat, should be clearly made known to the consumer. This would save highly food-allergic persons from much distress.

TABLE 53.—*Wheat-, Egg-, and Milk-free Diet*

The following foods are prohibited:

BAKING POWDER
Any that contains egg white or albumen. Read the labels.

BEVERAGES
Coffee cleared with egg white or egg shells. Coffee substitutes and other beverages made from wheat products. Root beer. Chocolate or cocoa unless made with water from milk-free and egg-free chocolate and cocoa preparations. Malted drinks, beer and ale. Any prepared drink made with eggs, milk or milk products or from powders containing wheat, eggs, milk or milk products.

BREADS
Any breads, rolls, muffins, biscuits and crackers except Ry-Krisp and those made at home without wheat products, eggs, milk or milk products.

BREADED FOODS
If the breading mixture contains wheat products, eggs, milk or milk products.

CEREALS
Wheat cereals and those containing wheat or wheat products. (Read labels carefully.) Use no milk or cream.

DESSERTS
Cakes, doughnuts, dumplings, fritters, macaroons, meringues, pastries; sherbets, ice creams, mousses, ice cream cones; bavarian creams, blanc manges and custards. Prepared mixes. Cookies, frostings and puddings unless made at home without wheat products, eggs, milk or milk products. Pies if fillings contain wheat flour or other wheat products, eggs, milk or milk products and crusts are made with wheat flour or wheat cereals.

EGG DISHES
Baked, coddled, creamed, deviled, scalloped, fried, poached, scrambled, shirred, hard or soft cooked eggs, egg drinks, egg sauces, meringues, souffles and omelets. Do not use dried or frozen eggs in any food. Do not use any mixture that contains eggs, egg powders, dried eggs or albumen.

FATS AND SALAD DRESSINGS
Butters and margarines. All salad dressings except true French dressing unless homemade without wheat products, egg, milk or milk products.

MEATS, POULTRY, GAME, FISH AND SEAFOOD
Swiss steak, croquettes, meat loaves; bread and cracker stuffings. Commercially prepared and dealer-prepared meats for they often contain wheat products, eggs, or milk products. Chili con carne, unless made at home without wheat products, eggs, milk or milk products.

MILK AND MILK PRODUCTS
Fresh, whole and skim milks. Cultured and buttermilk. Creams. Condensed, evaporated, dried milks and milk solids. Casein and lactalbumin. Butters and margarines. Curds and wheys. Powdered and malted milks. All cheeses.

MISCELLANEOUS
Creamed and scalloped foods. Foods prepared au gratin (with cheese). Rarebits, fritters and timbales. Foods dipped in batters. French toast. Malt products. Dumplings, noodles, spaghetti, macaroni, ravioli, mostaccioli, vermicelli, soup rings, alphabet and kindred products. Prepared mixes for biscuits, cakes, cookies, doughnuts, ice cream, muffins, pie crusts, puddings and waffles.

SAUCES AND GRAVIES
Hollandaise, tartar, egg, white, cream, butter and hard sauces. Any sauces or gravies thickened with wheat flour or containing egg, milk or milk products. Read labels on commercial sauces and do not use if they contain wheat products, eggs, milk or milk products.

SOUPS
Cream soups or any other soup containing milk or milk products. Mock turtle soup. Consommes, bouillons, broths or any soup cleared with egg or containing ingredients made with egg. Any soup thickened with wheat flour or containing wheat products such as noodles, soup rings or alphabet products, etc. Canned and dehydrated soups containing wheat products, eggs, milk or milk products.

SWEETS
All candies, except hard candies, unless made at home without wheat products, eggs, milk or milk products or unless the list of ingredients given on the labels of wrapped candies contains no wheat products, eggs, milk or milk products.

VEGETABLES
Creamed and scalloped vegetables and those prepared and served in any way with wheat products, eggs, milk or milk products.

WHEAT AND WHEAT PRODUCTS include: (1) all the following flours: white, bread, all-purpose, cake, pastry, self-rising, wheat, whole wheat, entire wheat, cracked wheat, graham, enriched, durum, phosphated; (2) also: wheat, wheat germ, bran, farina, semolina; (3) and in addition, cracker meal, bread crumbs, and malt.

EGGS include: fresh, frozen, egg powders, dried eggs and albumen.

MILK AND MILK PRODUCTS include: fresh, whole and skim milks. Cultured and buttermilk. Creams Condensed, evaporated dried milks and milk solids. Casein and lactalbumin. Butters and margarines Curds and wheys. Powdered and malted milks. All cheeses.

TABLE 53—*Continued*

The following foods are permitted:

BEVERAGES
Tea and coffee (unless cleared with egg or egg shells) served without milk or cream. Chocolate and cocoa made with water and milk-free chocolate and cocoa. Fresh, frozen and canned fruit juices. Mineral and carbonated waters.

BREADS
Ry-Krisp. Corn and rye breads made at home without eggs, milk or milk products.

CEREALS
All ready-to-eat and cooked cereals except those made from or containing wheat or wheat products—served without milk or cream. Fruit sauces can be served on cereal or dried fruits can be added to a thin cooked cereal.

DESSERTS
Plain, fruit-flavored and fruit gelatins. Fruit ices made with water. Tapioca pudding made without milk or eggs. Fruit fillings in Ry-Krisp Crumb Crust.

FATS AND SALAD DRESSINGS
Poultry, meat and vegetable fats and oils. Eggless French dressing. Read the label carefully on commercial French dressing for it may contain egg, egg powders, dried egg or albumen.

FRUITS
Fresh, frozen, dried, canned—raw and cooked without wheat flour or other wheat products, egg, milk or milk products.

MEATS, POULTRY, GAME, FISH AND SEAFOOD
All may be eaten if prepared without wheat products, eggs, milk or milk products. *Ry-Krisp stuffing can be used.*
(Caution: Canned and commercially prepared meats such as frankfurters, hamburger, meat loaf and sausages and some dealer-prepared meat patties frequently contain wheat and milk products.)

MEAT ALTERNATES
Dried peas, beans, lentils, nuts and peanut butter. Use no wheat flour or other wheat products, eggs milk or milk products in preparation.

MISCELLANEOUS
Chili powders, condiments, flavoring extracts, herbs, nuts, olives, pickles, salt and spices. Popcorn prepared without butter or margarine.

SAUCES AND GRAVIES
Catsups. Bottled sauces containing no wheat products, egg, milk or milk products. (Read the labels.) Homemade meat, vegetable and chili sauces and gravies prepared without wheat, eggs, milk or milk products.

SOUPS
Homemade meat, fish and vegetable soups prepared without wheat products, egg, milk or milk products. *Rice, barley and Ry-Krisp crumbs can be used for thickening.*

SUGARS AND SWEETS
Brown, granulated, powdered and confectioner's sugars. Honey, molasses, sorghum and syrups. Jellies, jams, marmalades and preserves. Hard candies and candies made at home without wheat, eggs, milk or milk products. Wrapped commercial candies containing no wheat products, eggs, milk or milk products in the list of ingredients.

VEGETABLES
Fresh, frozen, dried, canned—raw, or cooked without wheat products, eggs, milk or milk products. Salt, pepper and meat drippings can be used for seasoning.

In conclusion, it should be stated that the advantage of the elimination diets over the trial diet lies in the fact that during the search for the allergen the patient can be kept on an adequate and relatively varied diet. In order to combine this advantage with those of the trial diet, chiefly the saving of time, the present writer,[645] proceeding from the investigations of Luithlen,[646] has suggested the Specific Propeptan diet for identifying nutritional allergens.

4. SPECIFIC PROPEPTAN DIET

The term "Propeptan Diet" designates the procedure in which the protein contained in each individual food is "neutralized," so to speak, by the administration of the appropriate type-specific Propeptans.

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645. URBACH, E.: Klin. Wchnschr. **9:** 2406, 1930; Wien. Klin. Wchnschr. **43:** 503, 1930.

646. LUITHLEN, F.: Wien. med. Wchnschr. **76:** 907, 1926.

Food Propeptans are food digests derived from the individual foods through prolonged digestion with hydrochloric acid and pepsin, followed by some slight additional digestion with trypsin. Since the nature, chemistry, and immunologic properties of the Propeptans are fully discussed on page 260, the reader is referred to this section.

In practice the Propeptan diet is carried out by giving the patient a diet consisting only of those foods for which Propeptans are available. Since forty-eight different Propeptans are at the patient's disposal, the diet can be made as simple or as broad as he wishes or can afford.

It is essential that the Propeptan capsules be administered forty-five minutes before a meal. Because Propeptans are effective only when taken on an empty stomach, the food must be eaten at intervals of at least four hours. Small children may be fed every three hours, thus giving them from four to five feedings daily. If the time between meals is too long for the patient, he may be given sugar now and then during these periods.

Technic. One Propeptan capsule for each food is taken with a small amount of water exactly forty-five minutes before a meal. In cases of extreme hypersensitiveness to a certain foodstuff, it may be necessary to ascertain the tolerance to the Propeptan by giving one tenth or less of the contents of a capsule. It is absolutely essential that all the protein foods included in the meal should be "neutralized" by the appropriate Propeptans. Thus, it is not enough to give merely Beef Propeptan, for instance, before beef is eaten, because a meat dish may contain a number of other ingredients, such as flour, egg, onion, or spices, depending on whether it is stewed, breaded, fried, or prepared otherwise. If Propeptans for these ingredients are available, they must be administered simultaneously with the Meat Propeptan; when the Propeptans are not available, such ingredients may not be included in the preparation of the dish. In regard to bread, it is important to consider whether more than one type of flour was used in its manufacture. Since ordinary rye bread is made from both rye and wheat flour, the Propeptans for both have to be administered. Or if the bread contains corn, Corn Propeptan is necessary. In addition, one Yeast Propeptan capsule should be taken. Moreover, white bread often contains milk, and the crusts of rolls are glazed with egg, necessitating the use of the appropriate Propeptans. When butter is given, Milk Propeptan is indicated; when lard, Pork Propeptan. When vegetables are served, the corresponding vegetable Propeptans must be administered, and due consideration must of course be given to the various items used in preparing the dish (type of fat, flour, spices). It is not possible to discuss here all the instances in which protein items occur in masked form in various dishes (for further information see p. 272).

It will be seen from Table 54 that as many different Propeptan capsules have to be taken before a meal as there are foods containing proteins. Thus, in the examples given, four different Propeptans are taken before breakfast, nine before lunch, and nine before dinner.

If symptoms are only partially controlled, the desired effect can be achieved by increasing the dose to 2 or 3 capsules for the suspected allergenic food. In cases in which hypochlorhydria or achylia is present, the dissolution of the gelatin capsules may be unduly prolonged; hence the patient should be directed to open the capsule and to take the contents with a small amount of water. The same instructions should be given in the rare cases of hypersensitiveness to gelatin, and for small children who are unable to swallow capsules.

TABLE 54.—*Example of a Specific Propeptan Diet for Determination of Allergenic Foods**

Time	Propeptans	Time	Meal
7:15 a.m.	Orange, wheat, milk, yeast	8 a.m.	Orange juice, wheat cereal, white bread and butter, milk
11:15 a.m.	Beef, wheat, rye, yeast, potato, milk, cocoa, milk, apple	12 m.	Roast beef sandwich on rye bread, mashed potatoes, cocoa, applesauce
5:15 p.m.	Peas, lamb, carrots, rice, wheat, milk, yeast, cocoa, corn	6 p.m.	Split pea soup, broiled lamb chop, carrot, rice, white bread and butter, chocolate cornstarch pudding, milk

The following forty-eight Propeptans are available:
Meats: Beef, lamb, pork, veal, chicken,
Seafood: Flounder, oyster, shad, shrimp
Dairy products: Milk, American cheese
Eggs: Egg, egg yolk
Cereals: Barley, corn, oat, rice, rye, wheat
Vegetables: Asparagus, bean (baked, Lima, string, soy) cabbage, carrot, celery, lettuce, onion, pea, potato (white, sweet), spinach, tomato
Fruits: Apple, banana, grapefruit, lemon, orange, peach, pineapple, prune, strawberry
Nuts: Peanut
Beverages: Coffee, cocoa, tea
Yeast: Bakers' yeast

* Manufactured by Dalare Associates, 2300 Locust Street, Philadelphia 3, Pa.

If the objective and subjective manifestations of the allergy show improvement after five days of meticulous adherence to the Propeptan diet, the diagnosis of nutritive allergy is established. In order to determine the identity of the food allergen, one Propeptan after the other is omitted every second day, while the corresponding foodstuff is retained in the diet. Then, when symptoms reappear after ingestion of white bread without wheat Propeptan, for example, this bread is again given the following day together with the specific Propeptan. If the preprandial administration of the proper Propeptan again prevents the appearance of manifestations, the identity of one of the causative food allergens has been ascertained. In this manner, fourteen to twenty days of testing will usually suffice to identify the foodstuffs likely to act as allergens.

Since the complete Propeptan Diet test, as outlined above, may be too costly, Urbach[26] has elaborated a so-called limited Propeptan diet. This method consists of employing only a few types of Propeptans, at the expense of variety in the diet (only one meat, two vegetables, etc.). A limited Propeptan diet might require, for example, only eight types of Propeptans, such as wheat, yeast, milk, egg, beef, carrot, potato, and apple Propeptans. By the withdrawal of one of the Propeptans every second day, while the corresponding food is still ingested, hypersensitiveness to any one or more of the foods in question can be detected. After this procedure has been completed, the presence of other nutritional allergens may be ascertained by adding a new foodstuff every second day without the corresponding Propeptan. The sudden appearance of allergic manifestations will direct suspicion to the food item most recently restored to the diet. If strict adherence to the Propeptan diet does not result in improvement of the patient's objective and subjective manifestations, and when a nutritive allergy is still suspected, the next step consists of systematic elimination from the diet of carbohydrates, then of fats, and finally of salts as well as of acids. This procedure must surely lead to the discovery of the food allergen, if there is any.

5. LEUKOPENIC INDEX

Years ago, Widal reported that the leukocyte count is greatly decreased in acute allergic diseases. Joltrain interpreted this hemoclastic crisis test as positive when the decrease in the white corpuscle count exceeded 2,000 per cubic millimeter. Vaughan[588] employed this same principle to determine the presence of food allergy and on this basis elaborated a diagnostic procedure which he calls the leukopenic index (i.e., relationship between fasting and postprandial leukocyte count).

Technic. Two leukocyte counts, thirty minutes apart, are taken with the patient in a fasting state. Another white blood cell determination is made one to one and one half hours after ingestion of the suspected food, and compared with the fasting level. If the number of white blood cells after ingestion is 1,000 lower than before, the result is to be considered positive. To perform this test properly, at least five to six hours must have elapsed since the previous meal. Another important point is that all the counts should be taken by a single technician, using the same diluting pipets and counting chamber. Furthermore, it is essential that the patient strictly avoid physical exertion as well as psychic upsets (excitement) both before and during this test. Vaughan states that in 80 per cent of the tests the results correspond with the clinical symptoms. But, he concedes, repetition of the test quite often yields different results.

This method has been frequently checked and has met with considerable support as well as criticism. Gay[647] prefers the postdigestive leukocyte response to all other methods, such as elimination diets, food diaries, and skin tests. Rusten,[648] Rost,[649] and Schreus[650] have achieved excellent diagnostic and therapeutic results with this technic, particularly in allergic dermatoses. However, Brown and Wadsworth[651] studied over 2,000 leukocyte counts and concluded that there is no physiologic or pathologic justification for the use of the leukopenic index. Loveless et al.[652] disapprove of the method because in some cases they have observed a rise in the leukocyte count despite marked allergic symptoms following ingestion of known allergenic foods. Furthermore, there are disadvantages inherent in this method in that only one food can be tested in one day, and that it is not advisable to perform another test on the following day, since delayed reactions have not infrequently been observed.

The present writer is in full agreement with Vaughan, who, in his book, ends his discussion of the subject with these words: "We must conclude that the leucopenic index is still in the experimental stage and cannot be discussed at this time as a routine diagnostic procedure in allergy."

6. Accelerated Pulse Rate

Coca[632] observed that food-allergic individuals under the influence of an allergen exhibit an acceleration of the pulse rate, and he therefore advised a system of checking the pulse rate before and after ingestion of each food. Persistent acceleration means that the patient is allergic to the food eaten. Successful application of Coca's method requires a combination of trial diet and pulse control. The patient is placed on a sharply restricted diet for four days in order to establish the normal range of the pulse rate. Other foods are then systematically added to the diet, one after another, and their effect in increasing the pulse rate is carefully recorded. This specific acceleration varies in extent up to a maximum of thirty or more beats per minute above the normal upper limit for the individual, and it usually

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647. Gay, L. P.: J. A. M. A. **106:** 969, 1936.
648. Rusten, E. M.: Arch. Dermt. & Syph. **37:** 52, 1938.
649. Rost, G. A.: Klin. Wchnschr. **18:** 187, 1939.
650. Schreus, H. T.: München. med. Wchnschr. **86:** 1027, 1939.
651. Brown, E. A. and Wadsworth, G. P.: J. Allergy **9:** 345, 1938.
652. Loveless, M., Downing, L., and Dorfman, R.: J. Allergy **8:** 276, 1937.

occurs within one hour after ingestion of the allergenic food. Recently, Coca[653] has discussed some of the difficulties in interpreting the pulse-diet record which are encountered in the practical management of cases with food allergy. If further investigations substantiate Coca's observation, this method could become a very valuable diagnostic tool.

D. TREATMENT OF FOOD ALLERGY

When repeated tests with any of the methods mentioned above have established the allergenic role of one or more foods in a given case, the intolerance can be combated in various ways: (1) permanent or temporary elimination of the nutritional allergen; (2) specific hyposensitization by oral or parenteral administration of small, gradually mounting doses of the allergen; (3) specific deallergization by means of the skeptophylactic procedure; and (4) by synthetic diets.

Before discussing the various therapeutic procedures just enumerated we must consider briefly the difference in principle between the hyposensitization and the deallergization methods of treatment.

1. Difference between Hyposensitization (Desensitization) and Deallergization

By the hyposensitization procedure the antibodies circulating in the blood are markedly increased, while by the process of deallergization the tissue antibodies are neutralized. Thus, the difference between these two most important antiallergic approaches is a qualitative, and not a quantitative, one (Urbach and Gottlieb[653a]). Two examples will illustrate this.

Hyposensitization is accomplished, in the case of an individual hypersensitive to pollen, by a course of subcutaneous injections of pollen in small and systematically increasing doses every second or third day, with the result that the blood acquires an excess of specific antibodies. When this antigen is encountered later, it is so completely bound by the antibodies circulating in the blood that it cannot enter into contact with those of the tissues, which are the only antibodies leading to production of allergic manifestations. When the administration of antigen is interrupted, the antibodies are gradually eliminated from the circulating blood, but the tissue antibodies remain. Hence renewed contact with the antigens will, at a later time, again bring on an antigen-antibody reaction in the tissues, with its allergic consequences.

Deallergization, as used for clinical purposes, is effected chiefly by oral administration of small amounts of the antigen, followed later by a larger dose in order to call forth "microshocks" so mild that clinical symptoms are not produced. For example, on the first day of treatment an individual hypersensitive to iodide will be given 1 mg. of iodide by mouth and then 100 mg. forty-five minutes later, on the second day 2 mg. of iodide followed in three quarters of an hour by 150 mg., and so on until 500 mg. is tolerated. The first minute quantity of allergen produces within the organism a microshock that is strong enough to satiate the available supply of antibodies, thus resulting in a so-called negative or anergic phase. For the duration of this phase, newly introduced antigen encounters no antibodies and therefore cannot enter into an antigen-antibody reaction. Antibodies formed subsequently are immediately neutralized by the traces of the antigen remaining within the organism. This results, first, in a temporary state of insensitiveness, and then, following systematic repetition of the procedure, in a permanent state of insensitiveness due to the absence of antibodies.

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[653] Coca, A. F.: Ann. Allergy 2: 1, 1944.

[653a] Urbach, E. and Gottlieb, P. M.: Ann. Allergy 1: 27, 1943.

The hyposensitization and deallergization methods have in common the administration of minute quantities of antigen. While deallergization exploits the antianaphylactic principle to create the anergic phase, with arrest of production of specific antibodies as the ultimate objective, hyposensitization methods employ the device of quantitatively increased administration of antigen to achieve an increase in antibodies.

2. Elimination of the Nutritional Allergen

The most obvious and the simplest method of dealing with less commonly eaten foods, such as strawberries and lobster, is merely to eliminate them from the patient's diet. It is sometimes possible, notably in cases of recently acquired hypersensitiveness to protein, to restore tolerance by doing no more than excluding from the diet for a fourteen day period all animal protein and the principal vegetable proteins (e.g., legumes and bananas). At the conclusion of this interval patients will often be able to tolerate moderate quantities of the food which previously elicited allergic reactions (e.g., veal).

However, in cases involving hypersensitiveness to some virtually indispensable food, such as flour or eggs, which can hardly be eliminated from the diet for any length of time, it is advisable to undertake specific hyposensitization or deallergization.

3. Specific Hyposensitization by Administration of Small, Gradually Mounting Doses of Allergen

Schofield, in 1908, was the first to report treatment of severe allergy to egg by oral administration of minute quantities of this food in pills. His findings were confirmed by Schloss and others, but this therapeutic approach did not receive wider recognition until the extensive experimental work of Kesten, Waters, and Hopkins[654] had been published. These authors recommend an initial dose of 0.08 mg. of egg protein, 0.8 mg. of milk protein, and 1 mg. of other food proteins, the dose to be increased every fourth day. They specify that the dose is to be decreased if and when signs of intolerance become manifest. It is advisable to have the patient swallow even these small doses of protein in capsules, since direct contact of the allergen with the mucous membranes of the mouth and throat may bring on severe swelling. The course of treatment often lasts many months.

The present writer has obtained highly gratifying results with this method in some cases of dermatitis and neurodermatitis caused by food allergy. It is to be noted, however, that, after hyposensitization has been achieved, the patient must continue to eat the given food daily for some time. Moreover, this entire method is not only tedious and cumbersome, but actually dangerous in highly sensitive individuals. The following examples may serve to illustrate this point: severe general manifestations in an infant following oral administration of 5 drops of milk (Cathala et al.[655]); urticarial attacks after one drop of milk and edema of the lungs after several drops (Hopkins and Kesten[656]); dyspnea from a 1:100,000,000 dilution of egg white (Adelsberger and Munter[572]). The literature also contains several reports of death following minimal quantities of various foods. Thus Finkelstein,[657] Finizio,[658] Sales et al.,[659] Wason,[660] Hutinel,[661] and Campbell[662] described fatal reactions to milk, Halberstadt[663] to buttermilk, Bowen[664] to egg, von Starck[665] to peas, and Benson[666] to cottonseed meal. The present writer knows of the case of an infant who died from anaphylactic shock with intestinal hemorrhage following a few drops of milk.

Hyposensitization by the intracutaneous or subcutaneous route is therapeutically less effective and generally less reliable than the oral method, and it is even more dangerous. This becomes understandable in the light of such observations as the one reported by Gruetz,[667] who demonstrated that in a case of great hypersensitiveness to fish, a marked allergic

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654. Kesten, B. M., Waters, I., and Hopkins, J. G.: J. Allergy **6:** 431, 1935.
655. Cathala, J., Ducas, P., and Netter, A.: Bull. Soc. de pédiat. de Paris **31:** 224, 1933.
656. Hopkins, J. G. and Kesten, B. M.: Delib. 8th Internat. Congress. **8:** 602, 1930.
657. Finkelstein, H.: Monatschr. f. Kinderh. **4:** 65, 1905.
658. Finizio, G.: Pediatria **19:** 641, 1911.
659. Salès, G., Debray and Verdier: Bull. Soc. de pédiat. de Paris **21:** 372, 1923.
660. Wason, I. M.: J. A. M. A. **86:** 1322, 1926.
661. Hutinel: cited by Rowe[584].
662. Campbell: cited by Rowe[584].
663. Halberstadt, R.: Arch. f. Kinderh. **55:** 105, 1911.
664. Bowen, R.: cited by Rowe[584].
665. von Starck: Monatschr. f. Kinderh. **32:** 119, 1926.
666. Benson, R. L.: discussion to Bernton, H. S. et al.: J. Allergy **11:** 138, 1940.
667. Gruetz, O.: Arch. f. Dermat. u. Syph. **154:** 532, 1928.

reaction was elicited by intracutaneous injection of 0.000,000,005 Gm. of alcohol-precipitated protein derived from cooked fish. We have observed strong local reactions in individuals hypersensitive to egg following intracutaneous injection of a one to one hundred billion dilution of an egg white solution. For these reasons, the writer advises against the general use of the subcutaneous method of hyposensitization.

4. Specific Deallergization by the Skeptophylactic Procedure

The so-called oral skeptophylactic method of treatment is based on the principle that a hypersensitive individual can be protected against an anaphylactic reaction by taking a minimal dose of an allergenic food by mouth forty-five minutes prior to ingesting a larger quantity of the same food. Although only temporary protection is afforded at first, strict adherence to this method ultimately leads to complete deallergization in many cases. The phenomenon of skeptophylaxis can be explained on the basis of the antianaphylaxis theory of Besredka[668] (see below).

In practice, the skeptophylactic method can be carried out in either of two ways. First, if the identity of the food allergen is known, administration of minute quantities forty-five minutes prior to eating larger amounts is often effective. Theoretically, this method is perfectly sound. However, there are actually a number of difficulties, not the least of which is the fact that one cannot know what initial dose may be given with impunity. The second method, that of Propeptan therapy, is both simpler and more reliable.

Oral Treatment with Food Propeptans (Specific Food Digests)

I. EXPERIMENTAL BASIS OF PROPEPTAN THERAPY

In 1908, Besredka[668] demonstrated in a series of animal experiments that oral administration of minute quantities of an anaphylactogenic substance can achieve temporary protection against anaphylactic shock which would otherwise be expected to make its appearance, and that the anaphylactic state can be permanently eliminated by continuation of this treatment. Besredka then coined the term "antianaphylaxis" to designate the state produced by this specific action. The findings reported by Besredka were subsequently confirmed and enlarged upon by Richet,[669] and Grineff.[670] Lambert and coworkers[671] called this kind of protective treatment "skeptophylaxis" (from the Greek *σκηπτός*, "stroke of lightning," and *φυλαξίς*, "protection").

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668. Besredka, A.: Compt. rend. Soc. de biol. **65:** 478, 1908; Ann. de l'Inst. Pasteur **23:** 166, 1909.
669. Richet, C.: Compt. rend. Soc. de Biol. **70:** 252, 1911.
670. Grineff, D.: Compt. rend. Soc. de Biol. **72:** 344, 1912
671. Lambert, Ancel P. and Bouin, P.: Compt. rend. Soc. de Biol. **71:** 350, 1911.

In addition to specific skeptophylaxis, it was later learned that there was also such a thing as a nonspecific skeptophylactic effect. Auld[672] found that Armour or Witte peptones administered subcutaneously, intramuscularly, or intravenously bring about a nonspecific reduction in sensitivity. However, parenteral peptone therapy quite frequently has failed to obtain results in food allergies. Moreover, it is not entirely without danger to the patient because of the possibility of sensitization, and even of peptone shock (Roskam, Vallery-Radot et al.; Chiray). Therefore, Pagniez and Vallery-Radot[673] undertook oral treatment of allergic diseases based on hypersensitiveness to food by means of nonspecific peptones. In this manner they achieved satisfactory improvement in some cases of urticaria, lichen urticatus, and angioneurotic edema. Auld[674] and Luithlen,[646] however, reported many failures with this method. Results proved to be more satisfactory when Auld prepared peptones of animal and vegetable origin, and combined the two. It was Luithlen,[646] however, who was the first to realize that the inadequacy of the previous peptone therapy was due to the lack of specificity of the usual commercial peptones. He therefore rightly inferred that a strictly specific allergy to cow's milk, for example, could not be combated with meat peptone. He consequently suggested the preparation of various animal and vegetable type-specific peptones. Unfortunately, Luithlen did not have the opportunity to perform the necessary immunologic and clinical studies with the specific peptones, because he died prematurely.

The present writer,[645,675,676] after some years of experimental work, presented proof that in cases of specific food protein allergy only the type-specific food digests, which he named Propeptans, have a skeptophylactic effect. Moreover, he established the fact that these preparations are useful in the diagnosis of food allergy in addition to their value in treatment. First, a temporary deallergization is achieved which will become permanent if therapy is continued for two or three weeks. Lasting cures were attained by the present author in several hundred patients with food allergy. They include cases of urticaria, angioneurotic edema, dermatitis, asthma, rhinopathy, gastrointestinal allergy, and migraine, in which foods could be proved to be the causative allergic factor.

Propeptans are food digests derived from the individual foods through prolonged digestion with hydrochloric acid and pepsin, followed by some slight additional digestion with trypsin. They are composed of proteoses, peptones, subpeptones, simple peptides, and amino acids. While their allergizing effect is attenuated by this chemical action, they still retain the

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672. Auld, A. G.: Lancet **1:** 790, 1923; **2:** 67, 1932.
673. Pagniez, P. and Vallery-Radot, L. P.: Presse méd. **24:** 529, 1916.
674. Auld, A. G.: Brit. M. J. **1:** 696, 1921.
675. Urbach, E.: Med. Klin. **29:** 1435, 1933.
676. Urbach, E.: Wien. med. Wchnschr. **83:** 761, 1933.

specificity of the corresponding proteins. The Propeptans do not contain native protein (demonstrated by the absence of acid-precipitated nitrogen) as do the commercial peptones. Full details of the chemical composition of the Propeptans were presented by Urbach, Jaggard, and Crisman.[677]

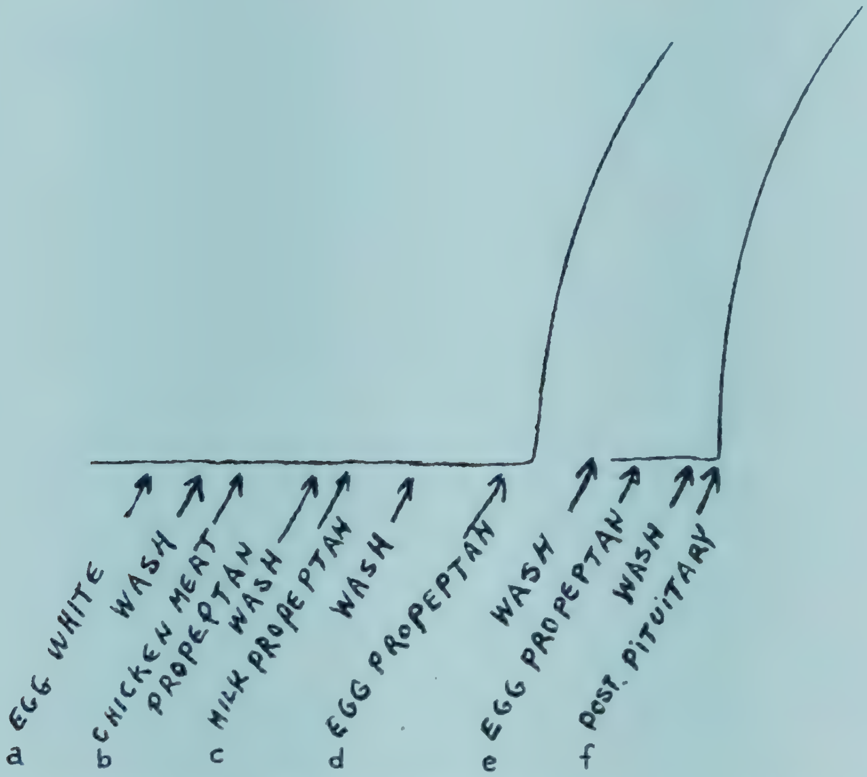

Fig. 82. Schultz-Dale Test Performed upon the Uterus of a Guinea Pig Allergized to Egg Propeptan

There was no reaction upon the addition of egg white (*a*), Chicken Meat Propeptan (*b*), or Milk Propeptan (*c*). However, the addition of Egg Propeptan (*d*) resulted in a violent reaction. There was no reaction to a second portion of Egg Propeptan (*e*), proving that the first reaction was specific for Egg Propeptan. The final reaction (*f*) was the result of posterior pituitary extract added as a check on the sensitivity of the uterus.

In view of the theoretical as well as practical significance of the strictly specific action of the Propeptans, it seems necessary to submit experimental proof of their specificity and of their skeptophylactically protective action.

With the aid of the Schultz-Dale expeimental procedure,[678] we were able to show that the uterus of an animal sensitized to Egg Propeptan is specifically hypersensitive in that it reacts neither to the substance from which the Egg Propeptan is originally derived—namely, egg white (Fig. 82a)—

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[677] Urbach, E., Jaggard, G., and Crisman, D. W.: Ann. Allergy **2**: 424, 1944.

[678] Urbach, E., Jaggard, G., and Crisman, D. W.: Ann. Allergy **3**: 172, 1945.

nor to the Propeptan derived from the muscle tissue of the same animal (Chicken Meat Propeptan) (Fig. 82b). Needless to say, therefore, it fails to react to Propeptan derived from any other species of animal (e.g., Milk Propeptan (82c); it reacts only and exclusively to the type of protein with which it was sensitized—e.g., Egg Propeptan (82d). The same type specificity can be shown in the lung perfusion test. The lung of a guinea pig sensitized to Egg Propeptan will react only to the addition of Egg Propeptan but not of egg, Chicken Meat Propeptan, and so forth.

The following case history will serve as a clinical and experimental demonstration of the strict type specificity of the Propeptans:

Edith D., aged 27, had been suffering since the age of 4 years from a recurring neurodermatitis of face, neck, and arms that gave practically no response to treatment. When questioned, the patient stated that she had been unable to eat eggs for several years because they invariably made her feel nauseated. Moreover, she observed that a strong local skin inflammation developed after she accidentally touched her eyelids with fingers that had come in contact with egg white in the kitchen.

The patient's statement as to the allergic skin response to chicken egg protein was readily confirmed experimentally. While the application of egg white to a clinically normal skin area evoked no objective or subjective manifestations whatsoever, application of the same substance to a skin area presenting neurodermatitic changes (the upper eyelids, for example) brought on a severe reaction after some twenty minutes (Fig. 83). This reaction, which was accompanied by extremely intense pruritus, consisted objectively of swelling of the skin and of such marked conjunctival injection that the lids were narrowed and there was profuse lachrymation and severe rhinorrhea. The hypersensitiveness was strictly type-specific; in other words, the raw white of goose or duck egg or horse serum failed to elicit any response.

However, when the patient was given two capsules of chicken Egg Propeptan by mouth forty-five minutes prior to the application of egg white to the eyelid, no objective or subjective manifestations appeared, either in the skin or on the mucosa, with the exception of mild itching (Fig. 84).

The type specificity of the Propeptans is best illustrated by the fact that not even Chicken Meat Propeptan was able to exert any protective action in preventing the appearance of reddening, swelling, and itching in the area to which the allergen had been applied. Similar observations have been made in numerous cases.

This constitutes conclusive proof of the type specificity of the Propeptans and establishes both experimentally and theoretically the basis for treatment and diagnosis with the aid of Propeptans.

In order to prove that this therapy is based on the skeptophylactically protective action of type-specific Propeptans, the writer, together with Jaggard and Crisman,[678,679] in an extensive series of animal experiments

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[679] Urbach, E., Jaggard, C., and Crisman, D. W.: Ann. Allergy 3: 287, 1945.

demonstrated that, when appropriately timed and given in suitable quantities, the oral, intravenous, or subcutaneous administration of Egg Propeptans to animals previously sensitized to egg white is capable of protecting these animals against otherwise certain death from anaphylactic shock. A Schultz-Dale test performed upon the uterus (Fig. 85) and a perfusion test upon the lung (Fig. 87) of a guinea pig allergized to egg white will elicit, upon addition of egg white, a violent reaction of both organs, indicating the presence of abundant antibodies and a high degree of hyper-

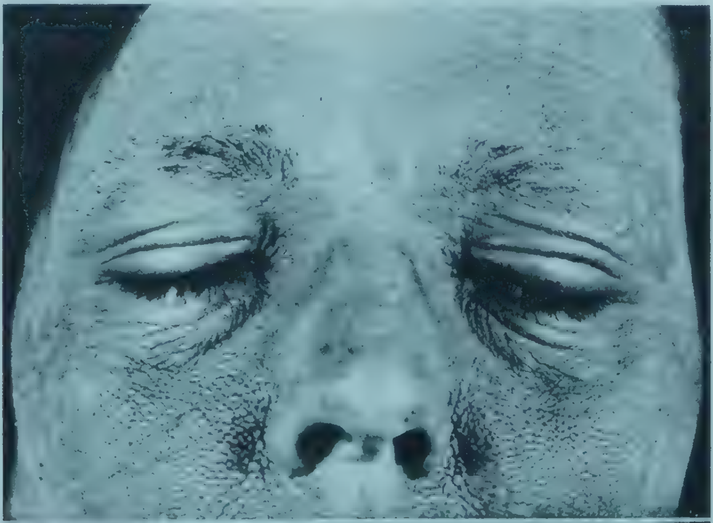

Fig. 83

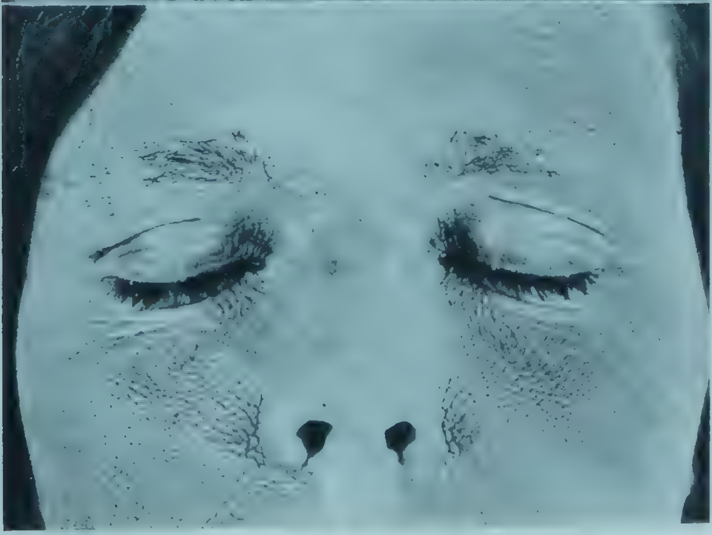

Fig. 84

Effect of Propeptan Therapy in a Case of Neurodermatitis

Fig. 83. Erythema and edema of eyelids produced by deliberate contact with egg white.

Fig. 84. Same patient, erythema and edema prevented by administration of 0.2 Gm. Egg Propeptan forty-five minutes before contact with egg white.

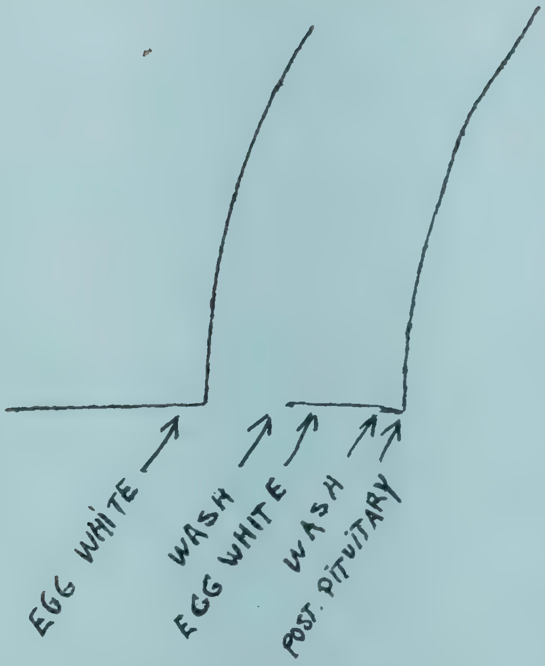

FIG. 85. SCHULTZ-DALE TEST PERFORMED UPON THE UTERUS OF A GUINEA PIG ALLERGIZED TO EGG WHITE AND RECEIVING NO PROTECTIVE TREATMENT

There was no reaction upon the addition of Egg Digest. A violent reaction followed when egg white was added, indicating a high degree of hypersensitiveness. There was no reaction to a second portion of added egg white, proving that the first reaction was specific for egg white. The final reaction was the result of posterior pituitary extract added as a check on the sensitivity of the uterus.

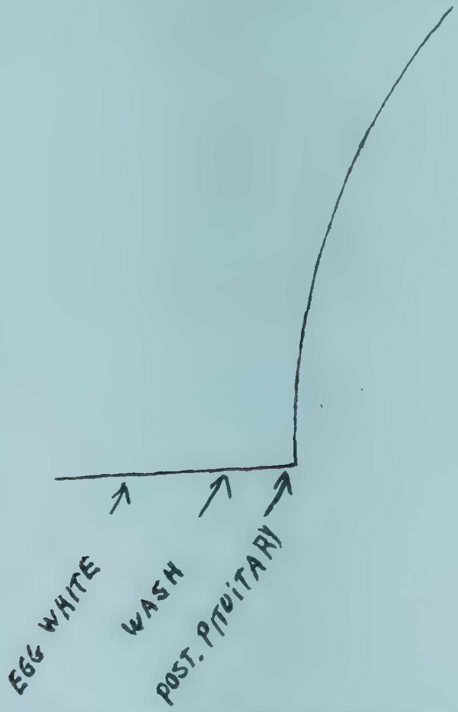

FIG. 86. SCHULTZ-DALE TEST PERFORMED UPON THE UTERUS OF A GUINEA PIG ALLERGIZED TO EGG WHITE, FOLLOWED BY PARENTERAL SKEPTOPHYLACTIC TREATMENT WITH EGG DIGEST

There was no reaction upon the addition of Egg Digest and no reaction upon the addition of egg white, indicating absence of antibodies in the uterus. Posterior pituitary extract was added as a check upon the sensitivity of the uterus.

sensitiveness. However, an animal that has received injections of Egg Propeptan prior to the administration of the shock dose of egg white

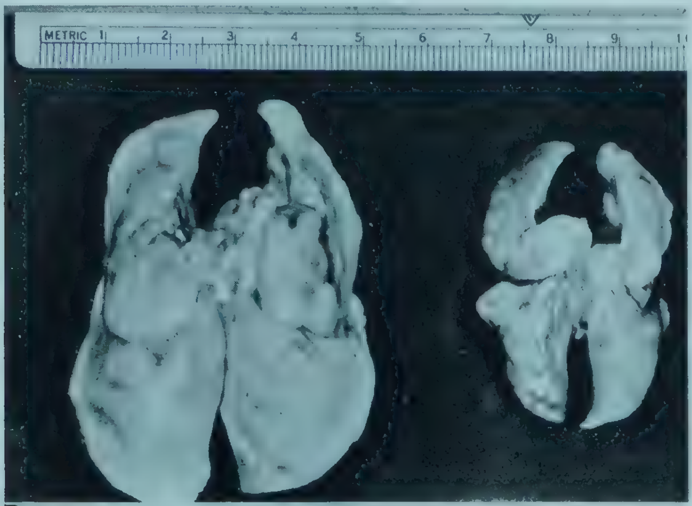

Fig. 87

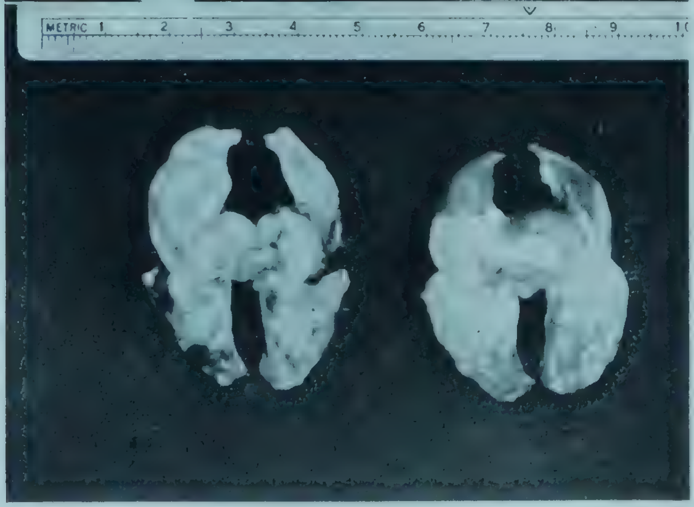

Fig. 88

Fig. 87. Lung Perfusion Test Performed upon the Lung of a Guinea Pig Allergized to Egg White and Receiving No Protective Treatment

The lung (left) showed huge inflation, indicating the presence of antibodies. A control lung of a nonallergized animal of the same weight (right) showed a negative reaction to the lung perfusion test.

Fig. 88. Lung Perfusion Test Performed upon the Lung of a Guinea Pig Allergized to Egg White, Followed by Parenteral Skeptophylactic Treatment with Egg Digest and Killed Six Hours after Receiving a Shock Dose of Egg White

The lung (left) showed no inflation, indicating the absence of antibodies. A control lung of a nonallergized animal of the same weight (right) showed negative reaction in the lung perfusion test.

parenterally will survive this lethal dose. If killed six hours later, it will show a negative Schultz-Dale test (Fig. 86) and a negative lung perfusion test (Fig. 88) demonstrating absence of antibodies and thereby indicating a state of insensitiveness, called deallergization.

Moreover, in guinea pigs allergized *orally* to native food proteins, in which allergic manifestations can be elicited by *oral* administration of the very same food proteins, these symptoms can be inhibited by means of *orally* administered Food Propeptans. In other words, guinea pigs are able to tolerate the oral shock doses of native food proteins when pretreated with Food Propeptans. That they have no antibodies in the organs is evidenced by the negative lung perfusion test. As shown by our experimental work,[678,679] Food Propeptans operate by inducing microshocks causing first partial and temporary, later complete and lasting, satiation of the antibodies, thus leading to deallergization.

It is highly probable that in everyday life oral deallergization in man is brought about mainly by physiologically formed degradation products such as proteoses and peptones of food products digested in the gastrointestinal tract. Since Propeptans are chiefly composed of proteoses and peptones, this therapy follows, so to speak, the example shown us by nature itself.

Table 55.—*Effect of Addition of Saponin on Degree of Enteral Allergization of Guinea Pigs*

Enteral Allergization (Feeding of 0.1 Gm. of egg white for seven days)	Interval	Concentration of Allergen (Dilution of egg white necessary for elicitation of anaphylactic shock, in 1 cc. doses)	Clinical Manifestations
Egg white alone	2 weeks after last previous ingestion	1:10,000	Fatal anaphylactic shock
		1:100,000	Slight pruritus
		1:10,000,000	No symptoms
Egg white +0.1 Gm. of glycyrrhiza each day		1:100,000	Fatal shock
		1:10,000,000	Fatal shock

In addition to establishing these principles, there is another point that warrants consideration here. In order to make the smallest possible amount of Propeptan suffice, the present writer added the saponin glycyrrhiza. This reduces the surface tension of the intestinal mucosa, which thereby becomes more rapidly and extensively permeable, thus increasing absorption (Table 55).

Nadel[680] undertook an exhaustive experimental investigation of this question and concluded that the oral administration of partially digested protein for skeptophylactic purposes, as in the case of Propeptans, is well founded, both theoretically and experimentally.

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[680] Nadel, A.: Ztschr. f. d. ges. exper. Med. **102:** 606, 1938; **103:** 446, 1938; **106:** 50, 1939.

In our opinion, Propeptan therapy is the method of choice for the control of every type of hypersensitiveness to food proteins, regardless of the clinical manifestations of the condition, whether as urticaria, colitis, asthma, or rhinopathy.

Lasting results obtained with this method within two or three weeks of treatment have been reported by numerous authors (von Eiselsberg;[681] von Eiselsberg and Klauders;[682] Hamamoto;[683] Hecht;[684] Herrmann;[685] Hopkins, Waters, and Kesten;[686] Kaemmerer;[595,687] Kitamura;[688] Markin;[689] Rehfuss;[690] Reiss;[691] Rusten;[692] Senn;[693] Shay;[694] Singer;[695] Schmidt;[696] Schreiber;[697] Schreus;[698] Ulrich[699]).

II. SPECIFIC PROPEPTAN THERAPY

After the identity of the food allergens has been established (see pp. 251–55), deallergization is undertaken in the following manner. The patient is told to eat once daily those foods which the Propeptan Diet or the trial or elimination diets revealed to be allergenic and to take previous to each meal the corresponding type-specific Propeptans. Each capsule contains 0.1 Gm. of Propeptan plus 0.02 Gm. of glycyrrhiza.* These capsules should be taken exactly three quarters of an hour before each meal. It is utterly useless to administer the Propeptans on a full or partly full stomach; therefore, there must always be an interval of at least four hours between meals (three hours in the case of small children). During these intervals, nothing except small quantities of water or perhaps some sugar may be consumed. In cases in which 1 capsule is not sufficient to control the symptoms, or if large quantities of the given food are eaten, 2 or more capsules should be taken at each meal for a few days. When treating infants or small children under 12 months, Propeptans without glycyrrhiza should be used. They are available on request.

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* A saponin derived from glycyrrhiza root; this is added to enhance the intestinal resorption.

681. Eiselsberg, K. P.: Wien. klin. Wchnschr. **45:** 332, 1932.
682. Eiselsberg, K. P. and Kauders, F.: Wien. klin. Wchnschr. **47:** 679, 1934.
683. Hamamoto, Y.: Orient. J. Dis. Infants **24:** 3, 1939.
684. Hecht, H.: Dermat. Wchnschr. **98:** 287, 1934.
685. Herrmann, H.: München. med. Wchnschr. **82:** 327, 1935.
686. Hopkins, J. G., Waters, I., and Kesten, B.: J. Allergy **2:** 239, 1931.
687. Kaemmerer, H.: Wien. klin. Wchnschr. **54:** 5, 1941.
688. Kitamura, S.: Jap. J. Dermat. and Urol. **39:** 87, 1936.
689. Markin, J. M.: New York State J. Med. **32:** 390, 1932.
690. Rehfuss, H.: personal communication.
691. Reiss, F.: Wien. klin. Wchnschr. **44:** 1598, 1931.
692. Rusten, E. M.: Proc. Staff Meet. Balyeat Clin. May 2, 1933.
693. Senn, W. N.: Clin. Med. and Surg. **39:** 612, 1932.
694. Shay, H.: personal communication.
695. Singer, A.: Wien. med. Wchnschr. **87:** 1020, 1937.
696. Schmidt, F. R.: personal communication.
697. Schreiber: Zentralbl. f. Haut- u. Geschlechtskr. **63:** 651, 1940.
698. Shreus, H. T.: Zentralbl. f. Haut- u. Geschelechtskr. **47:** 661, 1934; **60:** 99, 1938
699. Ulrich, G. R.: Ugesk. f. laeger **95:** 365, 1933.

The following case histories will present examples of how these principles are applied in practice. It must be stressed that in each case some variation in the dose of Propeptan required, the amount of food tolerated, and the duration of treatment will be encountered.

Case 1. A 16 months old boy had had recurrent asthma and vomiting since the age of 2 months. Symptoms ceased when cow's milk was eliminated from the diet. There was no history of allergy in the family. Administration of half a glass of milk produced vomiting in thirty minutes, followed by marked wheezing for several hours. Milk Propeptan and milk were administered as shown in Table 56. From Table 56 it can be seen that within two weeks the infant could tolerate half a pint of milk without Propeptans.

TABLE 56.—*Outline of Propeptan Therapy in a Case of Milk Hypersensitiveness*

Day	Milk Propeptan Capsules (0.1 Gm. each)	Milk (cc.) (45 min. later)	Symptoms
1st	1	10	Slight wheezing, diarrhea
2nd	2	10	Very slight wheezing
3rd	2	10	None
4th	2	20	None
5th	2	30	None
6th	2	50	Slight diarrhea
7th	2	50	None
8th	3	75	None
9th	3	100	None
10th	3	150	None
11th	3	200	None
12th	2	200	None
13th	2	200	None
14th	1	200	None
15th	0	200	None
Further, daily	0	250	

In cases of hypersensitiveness to several foods, all the corresponding Propeptans must be taken—for example, Milk, Egg, and Beef Propeptans when hypersensitiveness to these three foodstuffs has been discovered.

Case 2. A 30 year old woman with clinical symptoms of urticaria was found, with the aid of the Specific Propeptan Diet method, to be allergic to milk, egg, and beef. She was put on a normal diet including the three allergenic foods, which she was requested to eat twice daily, three quarters of an hour after taking two capsules of each of the appropriate Food Propeptans. Table 57 illustrates how the procedure was carried out. After five days all three foodstuffs were well tolerated. Thereafter the dose was reduced to one Propeptan capsule for each allergenic food. After two weeks of treatment, the patient was permitted to eat beef without Beef Propeptan. No objective or subjective symptoms ensued. Then milk was given without Milk Propeptan, and finally eggs without preprandial administration of the protective food digest.

When a patient is so extremely hypersensitive that even 1 capsule of Propeptan elicits clinical manifestations, the Propeptan must be administered in doses of 0.01 Gm. or, in exceptional cases, of 0.001 Gm., to begin with, diluted with sugar. A correspondingly small amount of the given foodstuff (for example, 1 Gm.) is to be given the patient forty-five minutes later.

The achievement of complete deallergization takes longer in some cases than in others. The average period of treatment is between two and three weeks. As already mentioned, the procedure in practice consists of giving the patient all the nontolerated food items once at first, later twice daily for a period of fourteen days, with preprandial administration of the proper Propeptans. During this period no attempt should be made to determine whether the hypersensitiveness has decreased or disappeared. But when the patient has been completely free from objective and subjective symptoms for fourteen days, the number of Propeptan capsules is gradually reduced until none are taken. If there has been hypersensitiveness to several foodstuffs, not all types of Propeptans are stopped at one time, but first the Propeptans of one type, and then, if no manifestations appear, the Propeptans of a second, then those of a third, and so on. The treatment is terminated only when the food or foods formerly not tolerated are taken with perfect impunity without preceding administration of Propeptans. If allergic manifestations appear, which rarely happens, another fourteen day period of Propeptan treatment is indicated. It is absolutely essential, furthermore, that for many weeks after the termination of treatment the patient take all the previously nontolerated foods (without Propeptans, of course) at least once daily in order to maintain his state of deallergization.

TABLE 57.—*Outline of Propeptan Therapy in a Case of Hypersensitiveness to Milk, Beef, and Egg*

Time	Propeptans	Time	Diet
7:15 a.m.	2 Milk, 2 Egg	8 a.m.	Fruit juice, cereal (with milk), coffee with cream, toast with butter, hard boiled egg
11:15 a.m.	2 Beef, 2 milk	12 m.	Roast beef sandwich, vegetable, ice cream
5:15 p.m.	2 Beef, 2 egg, 2 milk	6 p.m.	Roast beef, omelette, vegetables, chocolate milk shake

III. POLYPROPEPTAN THERAPY

In order to simplify the technic for the patient and to reduce the cost, a mixed Propeptan, called "Polypropeptan," has been prepared. Each capsule of Polypropeptan contains 0.05 Gm. of twelve different type-specific Propeptans (beef, chicken, egg, milk, rye, wheat, potato, spinach, pea, string bean, tomato, apple) plus 0.05 Gm. of glycyrrhiza.

The chief advantage of Polypropeptan therapy over that with individual specific Propeptans is that by taking 3 of these capsules the patient is permitted to eat anything within the limits of the twelve food items. He is thus freed from worry about eating something against which he has not, perhaps, been duly protected.

In practice, the Polypropeptan treatment proceeds in the following manner. When there is good reason to suspect the presence of a food allergy in a given case and it is not absolutely essential to know the identity of the allergens, the patient is given 2 or 3 Polypropeptan capsules exactly forty-five minutes before the mealtime. The diet may consist, at the patient's choice, of any of the twelve food items listed above. Since these capsules are ineffectual unless taken on an empty stomach, intervals of at least four hours must be maintained between meals (in case of small children, three hours). During these intervals, no food or liquid is to be taken except a small amount of water or a few sips of sugar water if desired.

TABLE 58.—*Outline of Polypropeptan Therapy*

Time	Polypropeptans	Time	Diet
6:45 a.m.	3	7:30 a.m.	Tomato juice, 1 hard boiled egg, cream of wheat, toast with butter, glass of milk
12:00 m.	3	12:45 p.m.	Chicken sandwich, milk, applesauce
5:45 p.m.	3	6:30 p.m.	Beef, potatoes, string beans, peas, bread and butter, milk, custard, apple

It requires a longer time in some cases than in others to accomplish permanent deallergization. The average period of treatment is three weeks. The patient is therefore to be instructed to adhere meticulously to the Polypropeptan routine for about this length of time. When the patient is completely free of all manifestations, he may be permitted to decrease the dose to two capsules, then one capsule per meal for a few days. Thereafter he may omit the Polypropeptan capsule before lighter meals (e.g., breakfast or a light lunch), until, finally, he is permitted to take his regular meals (restricted to any of the twelve food items) without having previously taken his capsules. If he remains asymptomatic, he is then to add a new food to his diet every second day. This is necessary, because foods other than the twelve contained in his diet may also be allergens.

In order to arrive at a varied diet more rapidly, the following procedure may be employed. If the patient is free of manifestations after one or two weeks of Polypropeptan treatment, he may add one new food every other day to his diet while still taking the Polypropeptans. The appearance of allergic phenomena means that the most recently added food is an allergen. This can be dealt with either by elimination of that food from the diet or by having the patient take the corresponding specific Propeptan (e.g., Tomato Propeptan) in addition to the Polypropeptan.

IV. SOURCES OF ERROR IN PROPEPTAN THERAPY

Not every failure of Propeptan therapy should be attributed to the method itself; it may be due to other causes:

(1) The case may not be one of food allergy. This question can be decided by placing the patient on a strict sugar diet consisting only of approximately 300 Gm. (10 oz.) of sugar per day, and water for two days. Only if there is rapid improvement can the condition be considered as a case of food allergy.

(2) While the patient may have food hypersensitiveness, this need not necessarily be in relation to proteins. It should be remembered that Propeptans can be effective only in allergies to proteins and are therefore useless in cases of hypersensitiveness to carbohydrates, fats, acids, or salts.

(3) Some patients present a combination of protein and nonprotein food allergies. Thus, the writer has reported a patient with severe lichen urticatus of ten years' duration which definitely improved on Propeptan therapy. However, after highly spiced or salted meals, relapses were noted. Mere elimination of salt and spices from the diet mitigated the itching but did not suffice to abolish it. However, the combined treatment resulted in a permanent cure within four weeks.

(4) It is essential that the factors predisposing to the allergy be searched for and, if possible, corrected. Thus, in cases of hypochlorhydria or achlorhydria the administration of hydrochloric acid and pepsin must accompany the Propeptan treatment. Either therapeutic measure alone will not be successful. Similarly, in the case of patients with chronic enteritis, an approprite diet is necessary along with the specific Propeptans. Furthermore, foci of infection in teeth, tonsils, and intestine must be considered, since not infrequently Propeptan therapy will remain ineffective until these are eliminated. Therefore, temporary withdrawal of Propeptans will be followed by recurrence of allergic symptoms.

(5) It must be remembered that in some cases many times the usual dose of Propeptan must be given in order to achieve cure. Thus, the writer has reported three cases, one of asthma, another of laryngeal edema and gastrointestinal symptoms, and a third with angioneurotic edema, due to food hypersensitiveness (egg and pea). In each instance large doses of Egg or Pea Propeptan, from 0.5 to 1 Gm. (i.e., 5 to 10 capsules), had to be

given before each meal in order to obtain freedom from symptoms. These large doses may soon be reduced (by 1 capsule daily), so that within two to three weeks the point is reached at which 1 capsule per meal is sufficient.

(6) On the other hand, in rare cases of extraordinary hypersensitiveness to a given protein, ingestion of even one-half dose of Propeptan may elicit allergic manifestations. In that contingency the treatment must be initiated with 0.01 to 0.001 Gm. of Propeptan.

(7) It should be borne in mind that a state of insensitiveness only newly achieved by Propeptan therapy may be annulled by ingestion of too large quantities of the allergenic food to which the patient had been rendered tolerant.

(8) Reallergization may take place as the result of any intercurrent infection, such as a "cold," or any gastrointestinal irritation due to alcohol, acute enteritis, excessive use of laxatives, or ingestion of very cold foods (iced drinks). The newly acquired allergization need not be to the same foods but may be to other ingestants, including drugs taken by mouth.

Finally, it should be stressed that Propeptan therapy must always be meticulously carried out. We suggest giving the patient a printed instruction sheet and a ruled blank* (Fig. 59) which he is asked to fill out and bring in at each visit. The physician is thus able to check and correct any mistakes he may have made. Errors are almost inevitable, especially in the beginning, despite the most painstaking explanations and instructions. Moreover, the physician should always keep in mind the possibility of minute quantities of certain forbidden foods being consumed by the patient without his knowledge, such as traces of egg in the crust of rolls, the milk contained in ice cream or chocolate candy, meat stocks in "vegetable" soups, wheat flour in "rye" bread, shortening in pies. Such examples of overlooked proteins constitute a common source of error and confusion, but this should not be charged against the method.

From these few examples it will be seen that complete understanding and scrupulous attention to detail are essential to the proper supervision of a course of Propeptan therapy.

5. Substitute and Synthetic Diets

Milk is an important food allergen in individuals of all ages, but it is in children in particular that it plays a major role. If evaporated cow's milk or goat's milk is not tolerated, milk substitutes may be used. Most popular of these are the various soy bean preparations, such as Sobee (Mead Johnson and Company), Mull-Soy (Borden Company), and Kreme O'Soy (Madison Foods). The soy bean emulsions are diluted with water in the same proportions as cow's milk would be diluted. Supplementary carbohydrate, in the form of cane sugar, is added in quantities of 2 to 4 tablespoons for the twenty-four hour formula. For infants over 5 months of age, the soy bean preparation is given in the form of a cooked cereal. This should be boiled for about an hour until it is quite thick and firm. Vitamins must be added to the formula, the synthetic preparations being preferable in order to avoid the occurrence of allergy to any protein in the sources from which the natural vitamins are derived, such as cod liver oil, liver, or yeast. Dependable synthetic vitamins include provitamin A (Carotene or Caritol, 8 to 10 drops), thiamine hydrochloride (0.25 mg.), riboflavin (0.5 mg.), nicotinamide (4 mg.), ascorbic acid (50 mg.), vitamin D (Viosterol or Drisdol, 8 to 10 drops), once daily.

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* Printed instruction sheets for both the Propeptan and the Polypropeptan therapy as well as ruled blanks may be obtained without charge from Dalare Associates, 2300 Locust Street, Philadelphia 3, Pa.

TABLE 59.—*Form for Patient's Food and Propeptans Record*

Hour	Propeptans	Hour	Diet	Patient's Remarks

Since a good many children develop a hypersensitiveness to soy bean preparations after a while, it is essential to have available milk substitutes, derived from cereals or vegetables. Wolpe and Silverstone[700] have devised nine such substitutes made from oats, barley, Lima beans, peas, taro, rice, rye, and corn flour with the addition of oil (cottonseed, olive, sesame, corn, and peanut), gelatin, dextrose, imitation vanilla, salt, crushed bone phosphate or calcium phosphate, 10 per cent aqueous solution of ferric chloride, and sometimes saccharin. Table 60 presents these nine formulas.

Stuart[700a] employs strained meats in formulas which are used as substitutes for cow's milk formulas. An example is shown in Table 61.

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[700] WOLPE, L. Z. and SILVERSTONE, P. C.: J. Pediat. **21:** 635, 1942.

[700a] STUART, G. J.: J. Allergy **16:** 253, 1945.

Table 60.—*Milk Substitutes in the Treatment of Allergies (Wolpe and Silverstone*[700]*)*

Constituents	Cups	Tbsp.	Tsp.	Diluted Formula	
Poya meal		7		P.	2.7%
Dextrose		9¾		F.	3.5%
Gelatin		5¾		CHO.	11.0%
Oil		4¾		Dilution ratio	
Bone phosphate or dicalcium phosphate			2¼ 4	1:4½	
Oat flour		12		P.	3.2%
Dextrose		6¾		F.	3.0%
Gelatin		4¼		CHO.	8.3%
Oil		4¼		Dilution ratio	
Bone phosphate or dicalcium phosphate			4 7½	1:5.6	
Barley flour		11		P.	3.1%
Dextrose		7¾		F.	3.9%
Gelatin		6		CHO.	9.1%
Oil		5		Dilution ratio	
Bone phosphate or dicalcium phosphate			4½ 8	1:4.87	
Rye flour	2	1		P.	3.4%
Dextrose		2		F.	3.5%
Gelatin		4		CHO.	9.9%
Oil		4		Dilution ratio	
Bone phosphate or dicalcium phosphate			3½ 6¼	1:4½	
Lima bean	¾	2¾		P.	3.2%
Dextrose		7¼		F.	3.1%
Gelatin		5		CHO.	9.3%
Oil		4		Dilution ratio	
Bone phosphate or dicalcium phosphate			4	1:5	
Dried peas		13		P.	3.3%
Dextrose		7¾		F.	3.0%
Gelatin		4		CHO.	10.6%
Oil		4		Dilution ratio	
Bone phosphate or dicalcium phosphate			4	1:5	
Soy flour	1½			P.	3.0%
Dextrose		8¼		F.	3.3%
Oil		2¼		CHO.	9.1%
Bone phosphate or dicalcium phosphate				Dilution ratio	
			3¼	1:5	

TABLE 60.—*Continued*

Constituents	Cups	Tbsp.	Tsp.	Diluted Formula	
Rice flour		15¾		P.	3.4%
Dextrose		5¾		F.	3.0%
Gelatin		6¾		CHO.	9.1%
Bone phosphate or dicalcium phosphate			4 7	Dilution ratio	
				1:5	
Corn flour	1	½		P.	3.0%
Dextrose		5¼		F.	3.1%
Gelatin		5		CHO.	9.3%
Oil		3¾		Dilution ratio	
Bone phosphate or dicalcium phosphate			4½ 7½	1:5	

TABLE 61.—*Strained Meats Used for Cow's Milk Formula Substitutes (after Stuart*[700a]*)*

	Weight Gm.	Measure	CHO	Protein Gm.	Fat Gm.	Calories	Ca Gm.	P Gm.	Fe Gm.	Cl as NaCl
Strained lamb	270	1⅛ cups		33	30	402	0.11	2.07	0.015	
P—12.23 per cent										
F—11.17 per cent										
Strained beef	307	1¼ cups		33	30	402				
P—10.74 per cent										
F—10.07 per cent										
Sesame or soy oil	10	2½ tsp.			10	90				
Sugar (cane or beet)	30	2⅔ tbs.	30			120				
Potato starch flour	24	2⅓ tbs.	20			80				
83 per cent CHO										
or										
Tapioca flour	23	2⅓ tbs.	20			80				
88 per cent CHO										
Calcium carbonate	3	1 tsp.					1.20			
40 per cent Ca										
Sodium chloride	1.75	½ tsp.								1.75
Water q.s. to 1,000 c.c.		4½ cups								
Total for 1,000 c.c.			50	33	40	692	1.31	2.07	0.0151	1.75
Or 100 c.c. per cent			5.0	3.3	4.0	69.2	0.13	0.20	0.0015	0.175
The above formula compared with whole cow's milk (Sherman and Bridges)			5	3.3	4.0	69	0.12	0.09	0.0002	0.175
Human milk (Bridges)			6.5	1.5	3.3	61.7	0.04	0.01	0.0001	0.058

The use of protein hydrolysates as a source of nitrogen for allergic individuals, and particularly for allergic infants and children, was suggested by the work of Shohl and his associates.[701]

Since the various proteins are composed of essentially the same amino acids, these authors assumed that the differences between these proteins must lie in their specific molecular organization as well as in the quantities in which the amino acids are present. The process of artificial digestion breaks down all proteins to the point where individual specificity of structure no longer exists. Hill[702] reports that thirty-six dermatitic infants, allergic to milk, were able to tolerate a protein hydrolysate preparation perfectly. The feeding mixture, which was given for as long as three months, contained 20 per cent of protein hydrolysate. Not only was the food well tolerated, but definite improvement of the dermatitis and satisfactory gain in weight were observed in nineteen of these infants. In one of these children who was allergic to milk and who presented not only an erythematous rash but also generalized nutritional edema, Beling and Lee[703] achieved a complete cure in fifteen days by giving a food mixture containing amino acids. Olmsted and co-workers[704] noted improvement in patients with high-grade food allergies who were given a mixture of 70 Gm. of amino acid, 140 Gm. of oil, 250 Gm. of dextrose, 20 Gm. of salt mixture, and synthetic vitamins. Since this synthetic diet has an unpleasant taste, a Levine tube was used to administer the feedings at intervals of two to four hours.

The present writer has employed Aminoids (Arlington Chemical Company), Amigen (Mead Johnson and Company), and Parenamine (Frederick Stearns and Company), in children allergic to milk. The results were most satisfactory in a number of instances, but in others the infants were so highly hypersensitive that they reacted to these digests, which, it must be remembered, contain traces of their higher protein constituents.

In cases of high-grade food allergy, where it is always a major problem to find enough suitable food items to nourish the patient, Alvarez[705] suggests that such individuals be sent in search of unusual foods in places which cater to immigrants. An allergic person is not likely to react too violently to a food which he has never eaten before, and which is botanically very different from anything commonly used as food in this country.

[701] Shohl, A. T., Butler, A. M., Blackfan, K. D., and MacLachlan, E.: J. Pediat. **15:** 469, 1939.

[702] Hill, L. W.: J. A. M. A. **116:** 2135, 1941.

[703] Beling, C. A. and Lee, R. E.: Arch. Surg. **43:** 735, 1941.

[704] Olmsted, W. H., Harfond, C. G., and Hampton, S. F.: Arch. Int. Med. **73:** 341, 1944.

[705] Alvarez, W. C., and others, editors: Help Your Doctor to Help You When You Have Food Allergy New York: Harpers, 1941.

CHAPTER V

Skin Diseases Due to Alimentary Infections and Alimentary Intoxications

When cutaneous eruptions make their appearance following ingestion of a certain food, it is often very difficult to determine just what role, if any, is played by food poisoning, food infection, food hypersensitiveness, or gastrointestinal disturbances caused by spoiled food, which in turn produce substances toxic to the skin.

Now that the tendency to use raw food has greatly increased the consumption of unpeeled fruits and of uncooked milk and vegetables, the incidence of diseases due to infected aliments has risen appreciably. This is particularly true of paratyphoid fever accompanied by exanthems and also of hoof-and-mouth disease. The latter diagnosis cannot be made, however, unless the characteristic systemic manifestations (fever, swelling, and slimy secretion on the lips and occasionally on the buccal mucosa and on the tongue, hypersalivation, oral fetor, and dysphagia) are accompanied by pustular inflammation of the nail-beds of the fingers and toes. Furthermore, diagnosis depends on the transfer tests (inoculation of blister contents into the plantar surface of a guinea pig foot), a positive test presenting a picture of local swelling, reddening, followed by vesicle formation. The writer has discussed this matter in some detail because there seems to be a widespread tendency to pronounce the diagnosis of hoof-and-mouth disease carelessly, merely on the basis of the appearance of aphthous stomatitis after drinking raw milk. According to Spaeth,[706] 63 per cent of all such infections are due to drinking raw milk from diseased animals, 0.5 per cent are caused by milk products, and the balance come from contact with cattle and other livestock. Gerlach[707] described a typical case which resulted from eating whipped cream and butter (Figs. 89, 90). It is interesting to note Hittmayer's report[707a] that an infection was caused by eating whortleberries growing on a hillside frequented by diseased cattle. Similarly, the disease can be contracted by chewing grass befouled by infected animals.

Avian tuberculosis is another infectious disease producing cutaneous manifestations (Figs. 91, 92). Loewenstein[708] demonstrated the presence

[706] Spaeth, H.: Therap. d. Gegenw. **65:** 56, 1924.

[707] Gerlach, F.: Wien. klin. Wchnschr. **37:** 210, 1924.

[707a] Hittmayer: cited by Spaeth[706].

[708] Loewenstein, E.: Wien. klin. Wchnschr. **37:** 231, 1924.

of numerous living bacilli in raw and even in soft-boiled eggs, which emphasizes the danger of infection from chickens infected with avian tuberculosis. Cases of avian tuberculosis in man reported by the present riter[709] were probably caused by eating raw eggs.

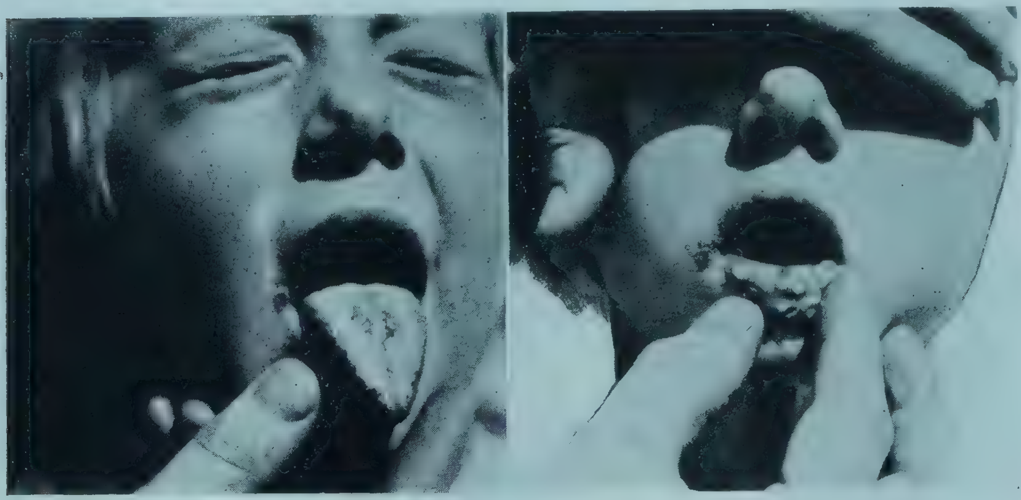

Fig. 89 Fig. 90

Figs. 89, 90. Hoof and Mouth Disease Resulting from Eating Whipped Cream or Butter from Infected Cattle

Tongue, lips, and oral mucosa present numerous vesicles filled with turbid fluid. The diagnosis was established by inoculation of guinea pig soles with vesicle contents, with resulting localized and later generalized manifestations.

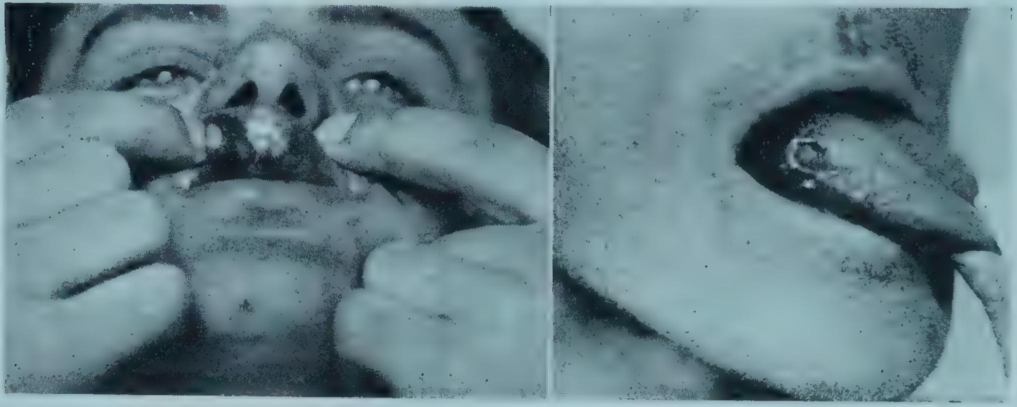

Fig. 91 Fig. 92

(Courtesy of Dr. Gerlach.)

Avian Tuberculosis

Fig. 91. Mucocutaneous lesions on the lip.
Fig. 92. Lingual ulceration.

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[709] Urbach, E.: Arch. f. Dermat. u. Syph. **157:** 360, 1929.

It seems likely, furthermore, that an occasional case of brucellosis infection may also be contracted directly from some food, the condition generally presenting a vesiculous (Fig. 93) or erythema multiforme-like picture with high remittent and long-lasting fever. We have urged,[710] therefore, that the possibility of this infection be borne in mind when one is confronted with skin manifestations resembling febrile erythema multiforme or dermatitis herpetiformis in patients coming from the country; and that a skin test with brucellergen be performed, in addition to the agglutination test. Cases in which infection with Brucella abortus could be definitely traced to some food have been reported by Giordano and Sensenich,[711] Nagorsen,[712] and others.

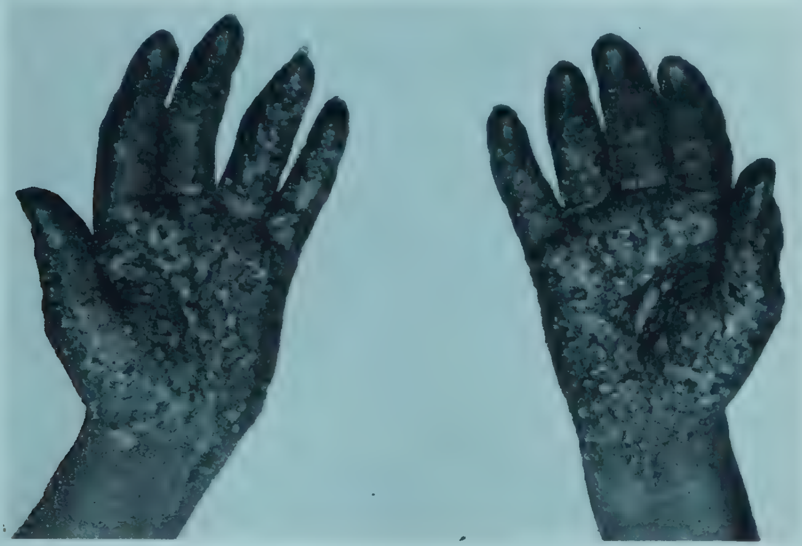

Fig. 93. Brucellosis of the Skin in the Form of a Vesicular Eruption of the Hands

Far more common, however, are the skin conditions caused by food poisoning. Food can have a toxic effect either because it contains an alkaloid of vegetable origin (mushrooms), or as a result of contamination with bacteria that produce deleterious changes in the food itself. While it was believed for many years that organisms of the Salmonella group were largely responsible for such food infections, other bacteria, notably staphylococci and occasionally streptococci, have more recently been incriminated. Food poisoning can manifest itself in from two to thirty-six hours after ingestion of the offending material, and with such symptoms as nausea, vomiting, abdominal pain, diarrhea, prostration, and various skin rashes, commonly of urticarial or erythematous character.

[710] Urbach, E.: Wien. klin. Wchnschr. **42:** 391, 1929.

[711] Giordano, A. S. and Sensenich, R. L.: J. Lab. and Clin. Med. **15:** 421, 1930.

[712] Nagorsen: Med. Klin. **26:** 1482, 1930.

Skin diseases due to alimentary intoxication may be either acute or chronic. The former often bear a close clinical resemblance to drug exanthems. Spoiled fish and meat, especially pork, as well as game that has been kept too long, spoiled or diseased shell-fish, mushrooms that have begun to rot, and old cheese can bring on a great variety of cutaneous and systemic manifestations, ranging through mild erythema, severe urticaria, and various forms of purpura (Figs. 94, 95), to a frank clinical picture of botulism.

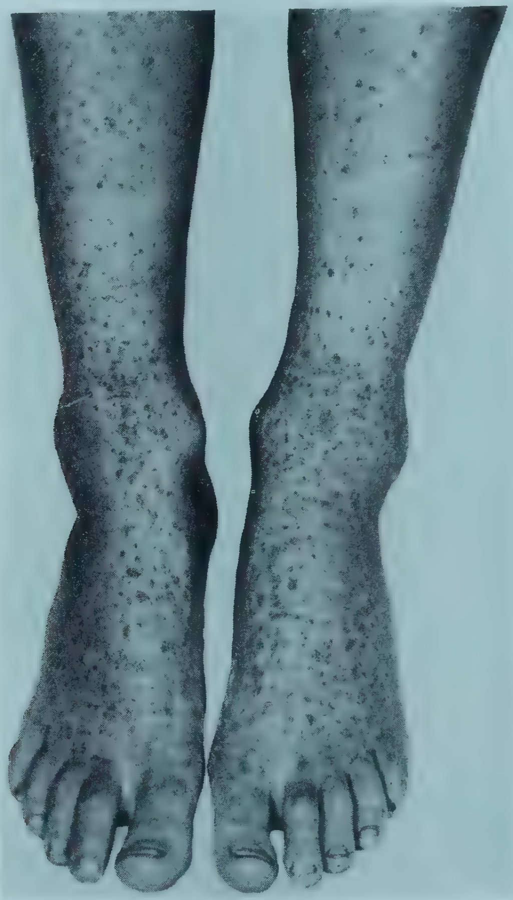

FIG. 94. GENERALIZED PURPURA DUE TO FOOD INTOXICATION

It is also important to remember that poisons produced in fish eggs during the spawning period in the spring of the year can be very dangerous when eaten. The disease often begins with urticaria, edema of the face, tongue, and fingers, followed by gastroenteritis and collapse. However, the drastic effects of these poisons seem dependent upon a certain degree of hypersensitiveness; furthermore, there are years in which these poisons are either absent or inactive. Their action is in no way related to what is known as "ichthyism," the generic term for poisoning caused by spoiled, decomposed, and possibly infected fish.

It is sometimes difficult to determine whether the intoxication in a given case is due to toxic properties peculiar to the food itself, to poisons used incident to pest control or disinfection of food or water, to bacterial toxins formed by bacterial action, notably on protein-rich foods, or to an underlying food allergy.

The first group includes, for example, the cases mentioned in Sticker's report.[581] He observed that some individuals suffer from a severe pruritic eruption, sometimes accompanied by renal and bladder irritation, following ingestion of the fruit of the Indian mango tree; and that others develop a vesicular inflammation of the lips, which sometimes assumes the proportions of an ulceration, after biting into the manzanilla apple. The dangerous part of the fruit is its milky juice. Susceptibility to the action of these poisons seems to be fairly widespread, but some individuals are affected far more severely than others. Oppenheim[712a] reports a case of intoxication which expressed itself in the form of an exanthem, following excessive use of eucalyptus candy for therapeutic purposes.

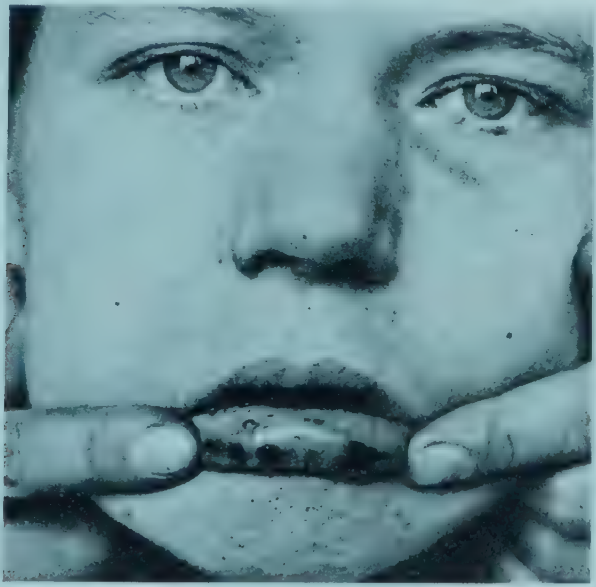

Fig. 95. Hemorrhagic Exanthem Following the Excessive Use of Saffron Taken to Produce Abortion

Every effort must be made to ascertain that the intoxication is attributable to the given food itself and not to bacteria or insects living on the plant and unwittingly eaten together with the food. Thus, as Matignon[713] has pointed out, the occasional cases of severe cutaneous manifestations and nervous disturbances following ingestion of *atriplex littoralis*, a weed growing in various provinces of China which is commonly eaten raw or as a salad, is apparently due to lice infesting this plant. Atriplicism, as this syndrome is called, is characterized by local swellings and sensory and trophic disturbances. Moreover, Martin,[714] Yu,[715] and Reiss[716] described cases of atriplicism due to *atriplex serrata*, a weed which is eaten as a last resort in times of famine. Some hours after partaking of these boiled herbs marked edema of eyelids and face appears. Shortly thereafter, the hands and arms become tremendously swollen. The cases generally recover but sometimes death occurs.

[712a] Oppenheim, M.: Dermat. Wchnschr. **54**: 224, 1912.

[713] Matignon: De l'atriplicisme. Shanghai: Imperial Maritime Customs Medical Reports, 1898. 5th issue.

Mendelson[717] succeeded in demonstrating that a dermatitis of the lips, observed in three Siamese who were in the habit of chewing betel nuts, which progressed from reddening and scaling to depigmentation, was due to a fungus which he was able to cultivate from both the nuts and the cutaneous lesions.

The group of dermatoses due to food poisoning includes notably the cutaneous manifestations of chronic ergotism due to eating bread made from rye contaminated with the fungus Claviceps purpurea. A similar condition, known as ustilaginism, was first described by Mayerhofer.[718, 719] This has been encountered only in children and presents the same clinical picture as ergotism, the only difference being that the toxic principle of the fungus, secale cornutum, is not demonstrable in the former. On the other hand, Mayerhofer found that the cornmeal with which these children were nourished almost exclusively was heavily contaminated with corn smut. The manifestations of this disease consist of itching of the skin and mucous membranes, dry scaling of the palms (Figs. 96, 97) and soles, acropathies, acrogangrene, muscular weakness, spasmophilia, and hypertension with tachycardia. Elimination of the contaminated corn meal from the diet results in a surprisingly rapid cure of all but the cardiac symptoms.

Mention must also be made here of arsenic poisoning, specifically of those cases due to ingestion of food containing arsenic. Foodstuffs may acquire traces of arsenic in various ways. In nature, the highest concentration of arsenic occurs in seafood, particularly mollusks and crustaceans. Shrimp heads the list, over 40 mg. of arsenic trioxide per Kg. of fresh material having been found (Bridges[169]). Petren[720] has reported cutaneous manifestations due to ingestion of fish or the water from certain lakes in Scandinavia which have a fairly high arsenic content. In some localities, especially in the proximity of mines, the soil is rich in arsenical min-

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714. Martin, S. H.: Chinese M. J. **39:** 809, 1925.
715. Yu, K. Y.: Chinese M. J. **49:** 148, 1935.
716. Reiss, F.: personal communication.
717. Mendelson, R. W.: J. Trop. Med. **27:** 284, 1924.
718. Mayerhofer, E.: Wien. klin. Wchnschr. **43:** 1077, 1930.
719. Mayerhofer, E. and Dragisic, B.: Ztschr. f. Kinderh. **59:** 543, 1938.
720. Petren, K.: Acta med. scandinav. **58:** 217, 1923.

erals. Ayres and Nelson[721] have pointed out that root vegetables and spring water may thus be subjected to contamination. A certain mineral water, widely advertised in California for drinking purposes, contains traces of arsenic (0.02 part per million) (Hamilton[722]).

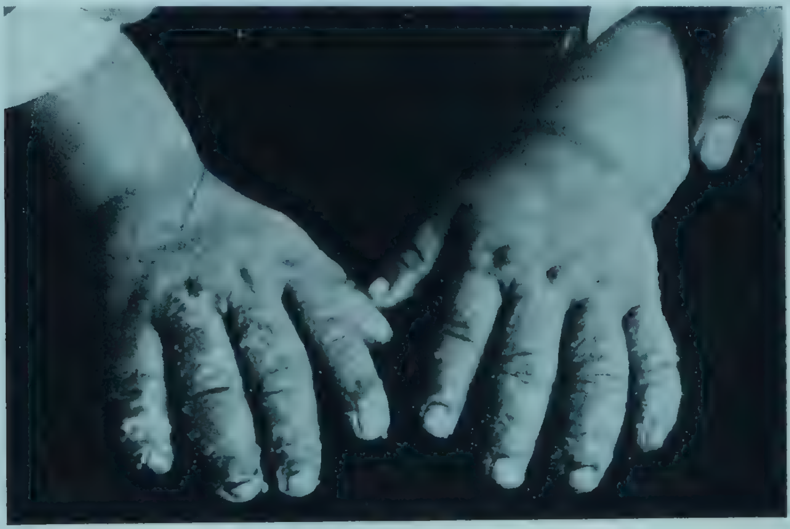

FIG. 96

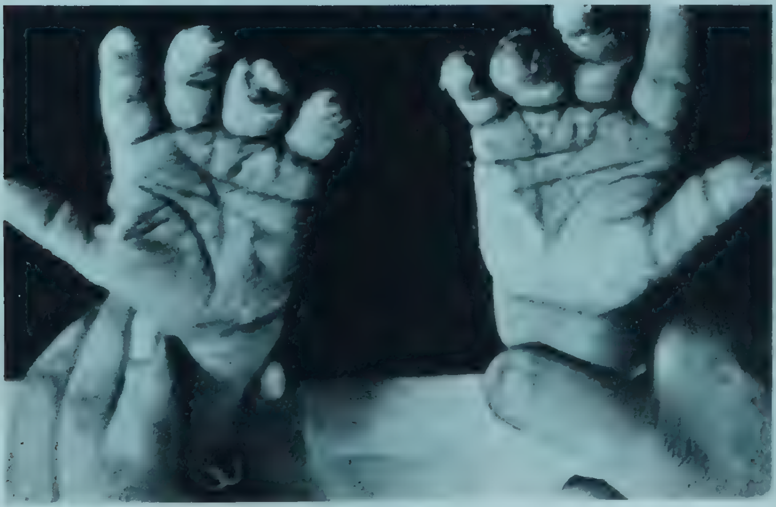

FIG. 97

SKIN MANIFESTATIONS DUE TO USTILAGINISM

FIG. 96. Demonstrating the dry scaling on the fingers.

FIG. 97. Case of longer duration, showing gangrene of the distal parts of the fingers.

(Courtesy of Dr. E. Mayerhofer.)

Far more common, however, are the skin diseases due to arsenic used as a spray for the control of insect pests on vegetables (particularly asparagus, broccoli, cabbage, cauliflower, celery) and on fruits (especially apples, blueberries, cherries, grapefruit, grapes, oranges, peaches, pears, and plums). When improperly applied and incompletely removed, these spray residues constitute a definite menace to health. Yeast exhibits a marked tendency to absorb arsenic from hops during the manufacture of beer. Wines, cider, and other fruit juices may contain appreciable amounts of this element. Canned and foil-wrapped foods are often contaminated with arsenic, which is also regularly present as an impurity in commercial glucose and in the shellac coating applied to confectionery. Traces of arsenic are generally found in Epsom salts and not infrequently in baking powder, and they are also often encountered in such a variety of items as egg powder, self-raising flour, cocoa, cheap candy, certain proprietary baby foods, and gelatin (Myers and Throne[723]). It is interesting to note that the aluminum sulfate used for the purification of drinking water in Illinois has been found to contain 1 to 3 parts per million of arsenic (Bartow and Bennett[724]).

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[721] AYRES, S. JR. and NELSON, P. A.: Arch. Dermat. & Syph. **30:** 33, 1934.

[722] HAMILTON, A.: Industrial Poisons in the United States. New York: The Macmillan Co., 1929.

The symptoms associated with chronic arsenic poisoning include recurrent generalized dermatitis (Fig. 98) with or without brownish pigmentation, pruritus, hyperkeratosis of the palms (Fig. 99) and soles (Fig. 100), alopecia, burning and tingling sensations in the extremities, neuritis, general weakness, dyspepsia, vertigo, and disturbance of locomotion.

An epidemic of arsenic poisoning due to beer was reported by Brooks and Roberts.[725] The beer had been brewed with fermented potato sugar, produced by hydrolysis of potato starch with the aid of sulfuric acid containing arsenic. An instance of mass poisoning, with severe cutaneous manifestations, involving virtually the entire crew of a French merchant vessel and attributable to a certain batch of wine, was described by Muehlens,[726] Tropp and Rauch,[727] and Thorel and Vinzent.[728] A case of generalized exfoliative dermatitis, following consumption of a considerable amount of whisky of doubtful quality, was reported by Ayres and Nelson.[721] Arsenic was found both in the patient's urine and in the whisky. The chronic arsenic poisoning so commonly seen in winegrowers is generally due to drinking a special kind of homemade wine. In some regions it is an old custom among winegrowers to produce a special vintage, strictly for their own consumption, by subjecting the grapes a second time to hard pressure. The juice and the pulp thus obtained, which naturally contain quantities of unclean waste material from the grapes that have

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723. Myers, C. N. and Throne, B.: New York State J. Med. **29:** 1258, 1929.
724. Bartow, E. and Bennett, A. N.: Illinois State Water Survey, No. 13. Urbana: University of Illinois, 1916.
725. Brooks, H. G. and Roberts, L.: Brit. J. Dermat. **13:** 121, 1901.
726. Muehlens, P.: Deutsche med. Wchnschr. **58:** 854, 1932.
727. Tropp, C. and Rauch, G.: Dermat. Wchnschr. **95:** 1023, 1932.
728. Thorel and Vinzent: Ann. de dermat. **3:** 618, 1932.

been sprayed with arsenic, are allowed to ferment once again. Samples of this beverage have frequently been found to contain arsenic (von Pein[729]). An excellent method of determining the presence of arsenic in the skin consists of removing a small piece of skin by the punch-biopsy technic (p. 13) and then subjecting the specimen to spectrochemical analysis. Fig. 101 shows the arsenic-content of normal and pathological skin.

It may be advisable to include in this section dermatoses caused by bromides. While, strictly speaking, this halogen should be classed as a drug, it is so commonly taken as a beverage as to be considered in the nature of a soft drink. The consequence of this practice is sometimes a bromoderma (Fig. 102).

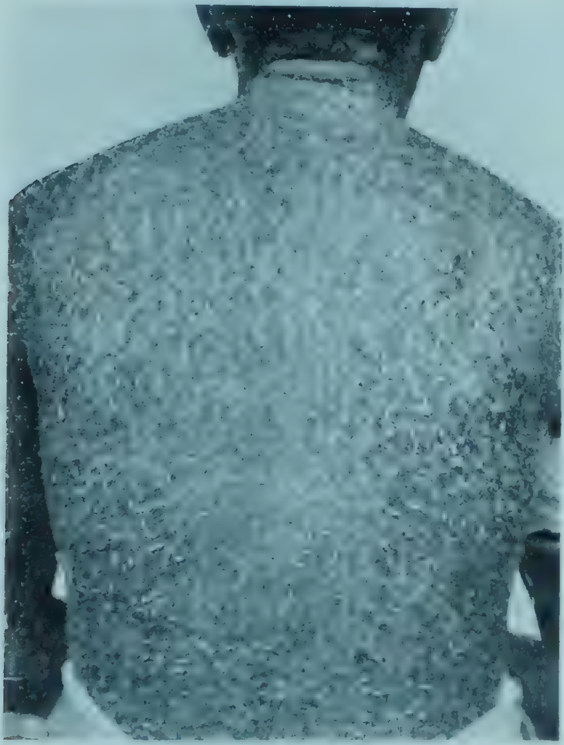

FIG. 98. GENERALIZED ARSENICAL DERMATITIS

The group of chronic alimentary intoxications leading to cutaneous manifestations properly includes those resulting from chronic overindulgence in alcohol. Many years ago Ehrmann called attention to the connection between excessive use of alcohol and dermographism, as well as pruritus, and reported rapid improvement of these dermatoses after alcohol had been discontinued. The possible explanation for this was discussed on page 230. Kreibich[730] described a case of purpura of many years' standing which he found to be demonstrably due to habitual drinking of large

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729. VON PEIN, H.: Deutsche Arch. f. klin. Med. **186:** 200, 1940.
730. KREIBICH, K.: Zentralbl. f. Haut- u. Geschlechtskr. **27:** 578, 1928.

quantities of beer. In a dermatosis bearing a close clinical resemblance to *erythrodermie pityriasique en plaques disseminées*, Urbach[731] was able to abate the symptoms by withholding alcohol and to bring on a recurrence by giving it to the patient. Gelbjerg-Hansen[732] has described trophic disturbances in the form of a perforating ulcer of the foot following excessive use of alcohol.

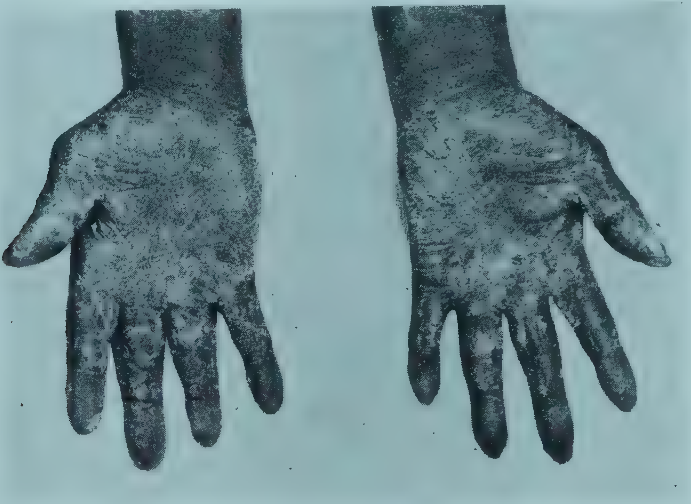

FIG. 99

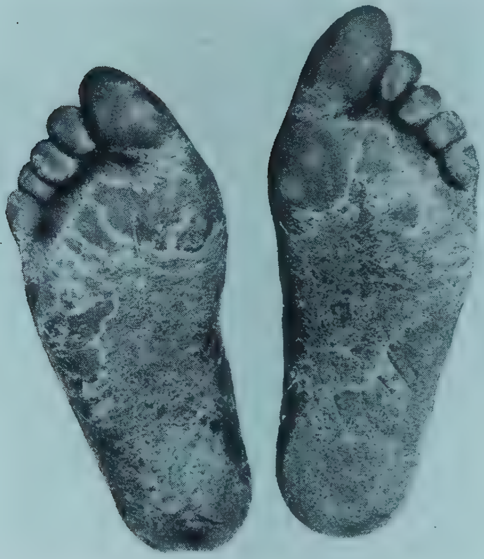

FIG. 100

ARSENICAL DERMATITIS

FIG. 99. Involving the palms.
FIG. 100. Involving the soles.

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731. URBACH, E.: Zentralbl. f. Haut- u. Geschlechtskr. **30:** 438, 1929.
732. GELBJERG-HANSEN: Zentralbl. f. Haut- u. Geschlechtskr. **34:** 284, 1930.

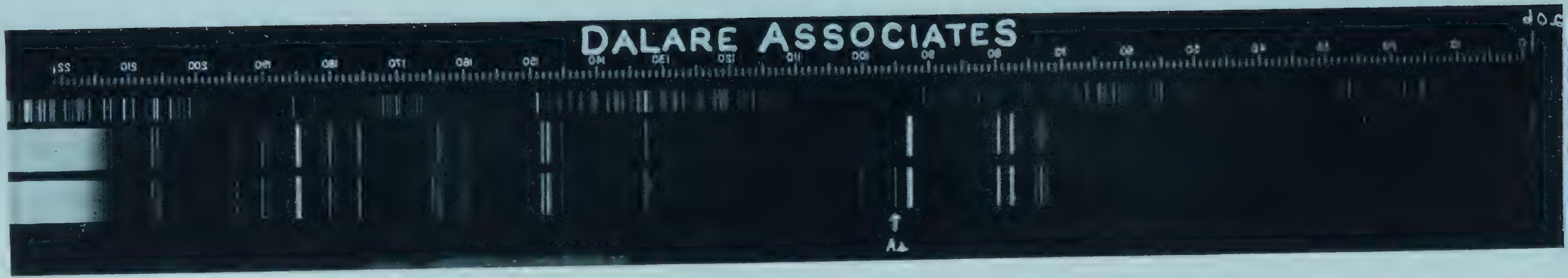
DALARE ASSOCIATES
As

FIG. 101. DETERMINATION OF ARSENIC IN THE SKIN BY SPECTROCHEMICAL ANALYSIS

Furthermore, it has been observed time and again that chronic overindulgence in alcohol (notably beverages of inferior quality) may, when accompanied by a diet low in calories and in vitamins and with exposure to strong sunlight, bring on a disease picture which is in all probability true pellagra. For a more detailed discussion of this condition, the reader is referred to the section on pellagra (p. 465).

Lastly, mention must be made of a group of skin diseases which have, to date, been observed only in animals, namely conditions which are caused by ingestion of photosensitizing substances contained in various plants. These diseases have been encountered almost exclusively in cattle, horses, pigs, and sheep, and are usually caused by buckwheat (*Fagopyrum*), St. Johnswort (*Hypericum*), wilted "dubbeltje" plant (*Tribulus*), clover (*Trifolium*), agave (*Agave lechuguilla*), and paintroot (*Lachnanthes*). Two principal entities are observed: fagopyrism and "yellow thick head." In fagopyrism, so termed because the symptoms were first observed following ingestion of Fagopyrum, only the white markings or the unpigmented skin areas are involved. The skin manifestations, consisting of intense itching, erythema, and swelling, are sometimes as severe as those of erysipelas, and are associated with a state of agitation. The symptoms are observed almost exclusively in the early spring, when the animals are turned out of their winter stalls into the fields, where they are exposed to sunlight. Other plants, particularly those of the Tribulus species, provoke progressive icterus, which is followed by hypersensitiveness to light, generally localized in the unprotected areas of the skin. Exposure to sunlight results in a severe inflammation of the skin, which then assumes a definitely yellowish color, whence the English term "yellow

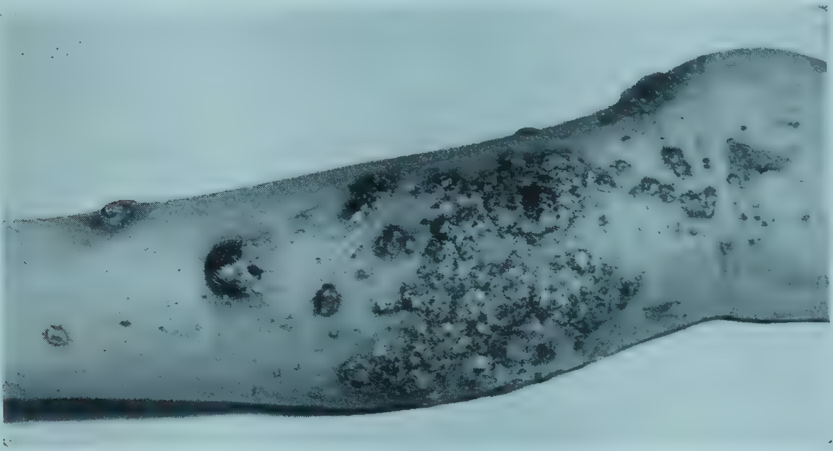

FIG. 102. BROMODERMA FOLLOWING HABITUAL USE OF BROMIDE PREPARATIASSON SOFT DRINKS

thick head" and the South African "Geeldikop" (Rimington and Quin[733]).

The sensitizing substance has been identified as phyllo-erythrin. This is a chlorophyl derivative formed in the sheep's rumen, probably under the influence of bacteria or protozoa.

With the exception of one doubtful case reported by Smith, fagopyrism in human beings is unknown. This is probably due to the fact that the active agent is altered in the cooking process, and thus becomes harmless. Nevertheless, there are cases of light hypersensitiveness in man apparently caused by ingestion of food containing photosensitizing substances. These are more fully discussed in the section on light hypersensitiveness (p. 514).

733. Rimington, C. and Quin, J. J.: Onderstepoort J. Vet. Sc. 3: 157, 1934.

PART THREE

INFLUENCE OF DISEASES OF THE GASTROINTESTINAL TRACT, LIVER, AND PANCREAS ON THE SKIN

The present chapter will be devoted principally to a discussion of those disturbances of the stomach, intestines, liver, and pancreas which impair normal digestion and absorption of ingested food, and thus promote or directly evoke cutaneous manifestations.

The relationship between an internal organ and the skin can no longer be considered merely from the viewpoint that anatomic lesions or functional disturbances of that organ may exert a harmful influence on the skin. Modern research has disclosed that this interrelationship is far more complex and that, indeed, three possibilities must always be considered: (1) the healthy skin may be affected by an anatomical or functional disturbance of an internal organ; (2) conversely, an anatomical or functional disturbance of the skin may affect healthy viscera; and (3) skin diseases and internal disturbances may be concomitant, either as a joint expression of some underlying systemic disease or as a purely coincidental occurrence. This concept applies particularly to the interplay between the gastrointestinal tract and the skin, the liver and the skin, and the pancreas and the skin. We shall therefore discuss this reciprocal action in the order outlined above.

CHAPTER VI

Dermatoses Due to Diseases and Dysfunction of the Gastrointestinal Tract

IT HAS long been a clinically established fact that gastrointestinal diseases can produce a variety of dermatoses such as dermatitis (eczema), neurodermatitis, urticaria, angioneurotic edema, pruritus, rosacea, acne, and seborrhea. Just what form the cutaneous repercussion takes in a given case would seem to be determined by the individual predisposition of the skin itself, rather than by the nature of the excitant.

In all skin diseases associated with gastrointestinal disturbances, the dermatosis may be due to any of the following possible etiologic factors: (1) toxic action on the part of the ingested food; (2) allergenic action of a food; (3) dysfunction of the digestive system; (4) anatomic disease of the digestive system; (5) action of toxins formed by pathologic bacterial flora; and (6) excessive absorption of skatol and other products of intestinal putrefaction. In addition, the interrelationship between disturbances of the digestive tract and cutaneous lesions may be brought about by nervous, endocrine, circulatory, and other mechanisms, as yet not fully understood (Stokes and Pillsbury,[734] Friedenwald and Morrison[735]).

Which of these various factors is to be incriminated in a given case? It must be frankly admitted that the investigative procedures now at our disposal do not always enable us to answer this question with any degree of assurance. Thus, for example, a food can produce skin manifestations as a result of the absorption of the toxic products which it contains; however, the spoiled food will, as a rule, also cause gastrointestinal disturbances. It is often difficult, therefore, to determine whether the intestinal inflammation and the skin manifestations are concomitant effects of the ingested toxic material, or whether the cutaneous condition is secondary to the noxious agents produced as the result of disturbance of gastrointestinal function. Another example is the possibility, stressed by Jadassohn[220] many years ago, that latent hypersensitiveness to a certain food may not become clinically manifest until some gastric or intestinal disturbance makes its appearance. Such abnormalities of the digestive organs may well lead to increased absorption of the allergen, through which, in turn, the cutaneous threshold of tolerance is reached, perhaps for the first time.

These few examples show that it is often almost impossible to distin-

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734. STOKES, J. H. and PILLSBURY, D. M.: Arch. Dermat. & Syph. **22:** 962, 1930.

735. FRIEDENWALD, J. and MORRISON, S.: Internat. Clin. **3:** 64, 1935.

guish between exogenous and endogenous factors. In many instances it is even a problem to localize the exact portion of the gastrointestinal tract where the disturbance actually takes place. In practice, it is often difficult to distinguish clearly between diseases of the stomach and those of the intestine because abnormal gastric secretions not infrequently bring about changes in the intestinal flora, which, in turn, lead to the formation and absorption of toxic materials in the intestine and thus ultimately to a dermatosis (Desaux and Antoine[736]). Many authors, therefore, quite simply refer to a "gastrointestinal disturbance" as the underlying cause of a given skin disease. However, for didactic purposes we shall endeavor to present the influence of each of the major parts of the gastrointestinal tract separately.

According to Bloch,[222] toxins such as may be produced in enteritis or colitis probably do not directly evoke skin diseases but cause them indirectly by altering the nature of the terrain, so to speak, making the skin susceptible to exogenous factors which, in turn, elicit the dermatosis.

In view of the fact that we shall frequently refer to the bacterial flora of the gastrointestinal tract, a short discussion of this subject is pertinent. The nature of the bacteria of the digestive tract is dependent upon the diet, gastric acidity and motility, external temperature, and other factors. While a luxuriance and moderate variety of organisms is met with in the mouth, the empty stomach is generally sterile. Although numerous organisms are ingested with the food, most appear to be destroyed rapidly, provided there is adequate gastric acidity and the motility of the stomach is not excessive. The normal duodenum, jejunum, and most of the ileum are relatively sterile, the few organisms which are present being largely enterococci* (Nissle[737]). In the lowermost segments of the ileum there are micro-organisms evidently brought there by the back flow from the colon, which teems with a multitude of bacteria. The flora of the large intestine is discussed in some detail on page 317.

The reason for the relative freedom of the small intestine from bacteria is evidently the antiseptic power of the gastric juice. Mutch[738] inferred that since the upper portions of the intestinal tube are laden with food products, the presence of many organisms in the small bowel would result not only in much waste but in the production of highly toxic products due to bacterial action on the food. On the other hand, an abundance of the bacterial flora of the colon appears to be necessary for rapid destruction of food residues which have no further nutritional value.

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* According to many bacteriologists, particularly the French, the enterococcus is a streptococcus found in the normal human intestine and characterized by its occurrence as pairs of ovoid cocci, sometimes in short chains.

736. Desaux, A. and Antoine, E.: Nutrition **6:** 55, 1936.
737. Nissle, A.: in Handb. d. pathogenen Mikroorganismen, by Kolle and Wassermann **6:** 391, 1928-29.
738. Mutch, N.: Brit. J. Surg. **2:** 608, 1915.

A. DERMATOSES CAUSED BY DISEASES OF THE STOMACH

In the opening paragraph of this chapter we mentioned a number of dermatoses which are sometimes associated with diseases of the stomach. There are three types of gastric conditions which are generally held responsible for cutaneous manifestations: (1) secretory anomalies; (2) disturbances in motility; and (3) inflammation of the mucous membrane, resulting from chronic irritation or infections, which makes the mucosa abnormally permeable.

Among the secretory disturbances, anacidity and hypo-acidity are far more important than hyperacidity. That, at least, is the opinion of almost all authorities who have investigated gastric acidity in a wide variety of skin diseases. Spiethoff[739] found that from 50 to 80 per cent of his cases of urticaria, dermatitis, rosacea, and acne showed aberrations from the normal, generally in the form of hypo-acidity or anacidity, rarely in the form of hyperacidity. But it was notably Ehrmann[288] who stressed the significance of secretory anomalies, particularly in neurodermatitis and pruritus. He reported that 56 per cent of his series of 200 neurodermatitis patients showed lowering or absence of gastric acidity, while only a few presented hyperacidity. Our own findings[740] illustrate the significance of hypo-acidity and anacidity even more strikingly, since no less than 10 of 32 cases of neurodermatitis showed a complete lack of hydrochloric acid, while 13 of the remainder were markedly and 6 moderately low in acid. By gastroscopic visualization Usher[741] determined that 18 out of 19 rosacea patients presented gastritis of varying degrees of severity. As a rule, severe changes in the gastric mucosa were associated with achlorhydria.

Obviously, the pathogenetic role of a secretory disturbance can be recognized only when correction of the anomaly is followed by distinct improvement in the cutaneous manifestations. Ayres, Jr.,[742] Walsh,[743] Ehrmann,[288] Marchionini,[149] Dobreff and Popchristoff,[744] Urbach,[740] and others have observed that certain skin diseases showed a marked tendency to clear up more rapidly following administration of hydrochloric acid (Fig. 103). However, the present writer, as well as Walsh and Marchionini, has seen

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39 . SPIETHOFF, B.: Arch. f. Dermat. u. Syph. **90:** 179, 1908; München. med. Wchnschr. **59:** 991, 1912.

7740. URBH, E.: Arch. f. Dermat. u. Syph. **142:** 29, 1923.

741. USHER, B.: Arch. Dermat. & Syph. **44:** 251, 1941.

742. AYRES, S. JR.: Arch. Dermat. & Syph. **20:** 854, 1929.

743. WALSH, W. S.: Med. Rec. **88:** 699, 1915.

744. DOBREFF, M. and POPCHRISTOFF, D.: Arch. f. Verdauungskr. **56:** 179, 1934.

cases of dermatitis and urticaria with hyperacidity, in which the epidermal or cutaneous manifestations promptly disappeared following oral or intravenous administration of sodium bicarbonate. Ehrmann[745] explained the connection between dermatoses and diseases of the stomach in the following manner: Abnormal products resulting either from faulty digestion or from bacterial decomposition of food due to anacidity or hypoacidity penetrate into the vessels of the papillary layer of the corium and there produce transudation. Thus, cutaneous sensory and vasomotor nerves are irritated, and the foundation is laid for pruritus and urticaria factitia, which often accompany dermatitis. Thereafter, the dermatitis may appear in response to any external mechanical irritation.

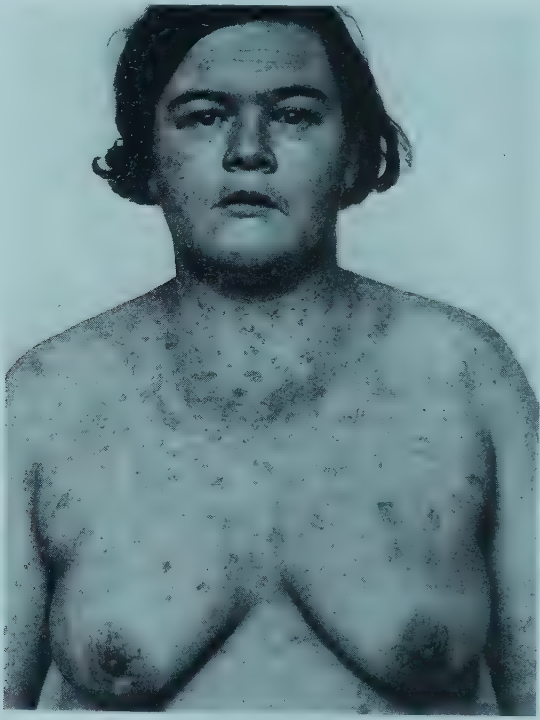

FIG. 103. URTICARIA DUE TO GASTRIC ANACIDITY

Completely alleviated by taking hydrochloric acid and pepsin.

It should be noted, however, that in dealing with cases of this kind the writer and many others have often failed to achieve any improvement in the cutaneous condition with hydrochloric acid therapy. These failures may be explained by the fact that the underlying cause is not the same in every case, and further by the fact that the secretory disturbance may often be, not the cause, but an accompanying symptom or even a consequence of the dermatosis. This will be discussed later in some detail.

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[745] EHRMANN, S.: Dermat. Ztschr. **25:** 283, 1918.

In order to understand clearly the fundamental significance of anacidity and hypo-acidity in the production of skin diseases it should be recalled that the gastric hydrochloric acid has four important functions: (1) to initiate the digestion of connective tissue and to disrupt the cell membranes of vegetable matter; (2) to activate pepsin for the first stage of protein digestion; (3) to cause retention of the food within the stomach until adequately digested and finely divided, through its action on the pyloric sphincter; (4) to disinfect the food in the upper segments of the intestinal tract.

While in hypo-acidity these functions of the hydrochloric acid are impaired, in achylia there is, in addition, inadequacy of gastric carbohydrate digestion, thus permitting considerable quantities of carbohydrate to reach the intestine without preliminary hydrolysis in the stomach. As the result of the deficiency in both the digestive power and the disinfecting qualities of hydrochloric acid, a pathologic intestinal flora is encouraged.

Since hydrochloric acid deficiency may also reduce the production of secretin by the duodenum, the pancreas is partially deprived of its hormonal stimulus, and this not uncommonly leads to a sharp reduction in the pancreatic secretion (hypochylia pancreatica). From this it is easy to understand why the intestine cannot properly cope with inadequately predigested food, thus giving rise to dyspepsia due to fermentation and decomposition, as well as to gastrogenous diarrhea. These latter conditions tend to make the intestinal wall abnormally permeable and thus to promote the penetration of improperly digested protein material into the blood stream.

For therapeutic reasons it is essential to determine in each case whether the gastric condition is due to anatomic change or to some functional disturbance, and whether such gastritis as may be present is to be regarded as primary or secondary.

In addition to the secretory disturbances of the stomach, its motility must also be taken into consideration. We have not infrequently observed[740] (22 per cent) hyperperistalsis in association with anacidity in cases of neurodermatitis. Moreover, in our own material, one of every four neurodermatitis patients presented ptosis and elongation of the stomach associated either with atony or with hypotonicity. Ehrmann reported the case of a boy who suffered recurrences of dermatitis in his fourth, ninth, tenth, and eleventh years, always in connection with gastric atony.

In recent years gastroscopy has become a dependable method for determining the presence of acute or chronic gastritis, although subjective symptoms may be lacking and chemical and roentgenologic studies of the stomach may fail to reveal the true nature of the condition. Chevalier and Moutier,[746] notably among others, examined patients with urticaria gastroscopically and observed swellings of the mucous membrane of the stomach which could be regarded as the counterpart of angioneurotic edema of the skin, and which eventually disappeared without leaving any anatomic change and without having given rise to any subjective symptoms. In all of these cases, the edema was localized in the fundus. Edema of the antrum pylori, on the other hand, was generally accompanied by gastric manifestations. Other cases of urticaria presented atrophic gastritis, a condition in which the symptoms often respond admirably to iron therapy. By the gastroscopic method Chevalier also discovered the presence of gastric inflammation in occasional cases of dermatitis in which subjective symptoms were almost completely lacking, and in which gastric analysis and the roentgenogram revealed nothing abnormal.

Lastly, considerable interest has been displayed in the view that, under the influence of an acute inflammation or as a result of the cumulative damage caused by chronic irritation, the mucosa of the stomach becomes pathologically permeable, permitting the absorption of by-products which are otherwise not absorbable (Funck[747]).

Gutmann[566] points to coffee, tea, spinach, and spices as predisposing to allergy by virtue of their capacity to increase the permeability of the mucous membrane of the stomach. In a series of animal experiments, Arloing and collaborators[748] dissolved the protective mucous lining of the stomach by administering oxgall, thereby promoting the penetration of the walls of the stomach by undigested protein, and thus ultimately allergizing the animal. Similarly, Hajos[749] succeeded in eliciting an anaphylactic reaction by the oral route in guinea pigs sensitized to horse serum. The animals were given cognac, and shortly thereafter horse serum by mouth. With this method, Urbach and co-workers[678] have, in repeated experiments, succeeded in allergizing animals orally against various foods. In a series of quantitative experiments, Gutzeit[750] demonstrated the role of gastroenteritis in producing allergy to ingested protein. Small quantities of serum taken from a subject hypersensitive to fish were injected (Prausnitz-Küstner technic) into both healthy individuals and patients with gastroenteritis. When the healthy persons were subsequently given 50 cc. of a fish extract (i.e., specific antigen) through a stomach tube, there was no reaction at the site of the serum injection. The gastroenteritis

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746. Chevalier, P. and Moutier, F.: Ann. de dermat. et syph. **7:** 337, 1936.
747. Funck, C.: Nutritive Allergie in der Pathogenese innerer Erkrankungen als Nahrschaden Erwachsener. Berlin: Karger, 1930. 2nd ed.
748. Arloing, F., Langeron, L., and Spassitch, B.: Compt. rend. Soc. de biol. **90:** 1243 and 1245, 1924.
749. Hajos, K.: Ther. d. Gegenwart **67:** 525, 1926.
750. Gutzeit, K.: Verhandl. d. Gesellsch. f. Verdauungs- u. Stoffwechselkr. 11th meeting, p. 92, 1932.

patients, similarly treated, developed papules and erythema at the previously injected skin sites. However, when the test dose was quadrupled, the healthy individuals also reacted at the passively allergized skin sites. Barber and Oriel,[751] A. and M. Walzer,[752] and the present writer are of the opinion that gastric hydrochloric acid deficiency plays an important role in the creation of food allergies. This fact must also be remembered when treating conditions due to hypersensitiveness. In this connection, it is interesting to note the Walzers' findings, to the effect that the action of allergy-producing foods is definitely reduced by hyperchlorhydria and enhanced by achlorhydria. This indicates that under normal digestive conditions the substance capable of eliciting specific hypersensitiveness is either unable to penetrate the wall of the stomach or is destroyed. Lastly, we must not fail to mention that in Lortat-Jacob's[753] opinion undigested or incompletely digested food proteins can reach the blood stream through the erosions of gastric or duodenal ulcers, and thus allergize the organism.

B. GASTRIC DISTURBANCES DUE TO SKIN DISEASES

We shall here endeavor to show that disturbances of the metabolism of the skin may have repercussions in other parts of the organism, not the least important being the gastrointestinal tract, and that these effects may well lead to anatomic or functional disturbances. According to Puntoni,[754] suppression of the cutaneous secretory function by applying a coat of varnish to an experimental animal has particularly damaging effects on the stomach, causing hemorrhage and even autodigestion, and on the intestine (see below). He attributes this injury to the toxic and nervous factors arising as a consequence of the depressed secretory activity of the skin. In man, Jamada[755] has observed that dermatoses causing extensive denudation of the epidermis are accompanied by definitely subnormal gastric hydrochloric acid levels. He attributes this directly to the change in chlorine metabolism, due to the abnormally high secretion in the denuded skin areas and the resultant sharp reduction in the blood chlorides available for the mucous membranes of the stomach. Geber[756] is inclined to take a somewhat different view. In cutaneous inflammations experimentally induced by exposure of extensive skin areas to strong sunlight, he too observed a marked decline in the free hydrochloric acid levels in the stomach, which remained subnormal until the dermatitis had subsided; but Geber is of the opinion that, as a result of the condition of the

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751. Barber, H. W. and Oriel, G. H.: Lancet **2:** 1009 and 1064, 1928.
752. Walzer, A. and Walzer, M.: Arch. Dermat. & Syph. **17:** 659, 1928.
753. Lortat-Jacob, L.: Presse med. **33:** 1699, 1925.
754. Puntoni, V.: Boll. d. scienze med. d. Bologna **9:** 499, 1913.
755. Jamada, S. and Inoye, K.: Jap. J. Dermat. & Urol. Sept. 1912.
756. Geber, H.: Dermat. Ztschr. **40:** 163, 1923.

skin, substances tending to inhibit gastric secretion make their way into the blood stream.

Some authorities, however, have noted an increase in the secretory activity of the stomach, at least during certain phases of acute generalized dermatoses in man (Brown[757]) and during the course of induced dermatitides in experimental animals (Miyake[758]). This brings us to a series of observations, ranging from Lortat-Jacob's[753] that quite a few of his dermatitis patients complained of gastric disturbances suggestive of ulcer; to Bergmann's comment[759] that he has seen so many instances of pruritic dermatoses associated with ulcers of the stomach that he refers to a "cutaneous etiology" in ulcus; to Kaufmann[760] who has seen dogs with experimental chronic dermatitis simultaneously develop hepatic degeneration and juxtapyloric gastritis, both of which he attributed to the toxic action of the albumins formed in the diseased skin; and, finally, to Konjetzny,[761] who observed cases of toxic and sometimes even of ulcerous gastritis in association with cutaneous conditions involving extensive areas.

We see no reason for doubting any of these claims. For one thing, we now generally recognize the existence of what is known as "elimination gastritis" (Bourget), which results from the fact that certain substances (e.g., iodide, bichloride of mercury, lead) when applied to the skin are eliminated by the stomach, where they produce chronic gastritis. Of a similar character is the gastrointestinal ulceration following skin burns and the subsequent resorption of proteolytic products resulting from severe and extensive cutaneous damage (Curling).

On the basis of investigations carried out in a series of two hundred patients with acute and chronic dermatoses, H. and F. Voss[762] claim that there is a definite relationship between the extension and the inflammatory phase of skin diseases on the one hand and the degree of gastric acidity on the other. Acute generalized dermatoses, according to the Vosses, are regularly associated with hyperacidity; chronic conditions, with hypo-acidity or anacidity. Kumagai[763] arrived at similar conclusions. Voss and Voss explain the hyperacidity associated with acute, inflammatory skin diseases as a consequence of a sudden increase in histamine. When, however, the cutaneous condition becomes chronic the mucous membrane of the stomach gradually enters a histamine-resistant phase, which finds clinical expression in hypo-acidity or anacidity.

757. Brown, W. H.: Brit. J. Dermat. **37:** 213, 1925.
758. Miyake, I.: Delib. 9th Internat. Dermat. Congress **2:** 61, 1936.
759. Bergmann, G.: Wien. Klin. Wchnschr. **47:** 945, 1934.
760. Kaufmann, F.: Deutsche med. Wchnschr. **55:** 1745 and 1795, 1929.
761. Konjetzny, G. E.: Wien. klin. Wchnschr. **46:** 451, 1933.
762. Voss, H. and Voss, F.: München. med. Wchnschr. **84:** 1486, 1937.
763. Kumagai, T.: Jap. J. Dermat. & Urol. **46:** 94, 1939.

C. SKIN AND STOMACH DISTURBANCES AS CONCOMITANT SYMPTOMS OF SYSTEMIC DISEASE

Some twenty years ago, the present writer[710] suggested the possibility that certain cutaneous and gastrointestinal diseases might well be regarded not as mutually interdependent but rather as concomitant symptoms of an underlying disturbance of the vegetative nervous system. As Schmidt has pointed out, cases of this kind present a syndrome consisting of dermatitis, anacidity or hypo-acidity, and bradycardia. In some instances an intoxication constitutes the underlying etiology. Here the skin and the stomach both participate in the elimination of the toxic substance, as a result of which both organs suffer damage from the same cause and present clinical manifestations. Avitaminoses, such as niacin deficiency, can also exert this kind of influence on these two organs, as in pellagra and anacidity, for example. Such concomitance is even more pronounced in cutaneous and gastric conditions due to allergy. The writer[26] recalls a patient with a severe urticarial eruption accompanied by violent gastric pain. It was found on roentgenologic examination that simultaneous with the cutaneous and gastric symptoms there was an allergic hypersecretion by the gastric mucosa, the hypersensitiveness being proved to be due to lobster.

A number of authorities now subscribe to the view that dermal and digestive disturbances may be concomitant expressions of an underlying systemic condition. Thus, Chevalier and Moutier[746] reported that, particularly in certain kinds of dermatitis, gastroscopic examination disclosed changes chiefly in the form of *plaques vesiculeuses* in the mucous membrane of the stomach, similar to those presented by the skin. These authors interpreted the cutaneous and gastric lesions as expressions of one and the same process, differing only in their localization. In a case of severe urticaria, Gaté and collaborators[765] found changes in the gastric mucosa. All these authors arrived at the conclusion that the gastritis and the dermatoses are parallel manifestations of an underlying systemic disturbance. The basis for this opinion is the similarity between the picture presented by the gastric mucosa and that by the skin (dermatitis, urticaria), and, further, the fact that the lesions of the stomach and those of the skin so frequently develop and then heal simultaneously. Bergmann[759] considers that form of gastritis which surrounds ulcers an "entodermatosis," basing this view on the fact that he has so often seen gastric or duodenal ulcers concurrent with pruritic dermatoses such as dermatitis, pruritus, and urticaria. Although we feel that this view may be somewhat extreme, we hasten to add that there should be a greater disposition to

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765. Gaté, J., Thiers, H., Chevallier, R. and Michel, P. J.: J. méd. Lyon 17: 369, 1936.

regard cutaneous and gastric disturbances as simultaneous manifestations, and to endeavor to manage these conditions from a broader, more general viewpoint.

D. THERAPY OF DERMATOSES DUE TO DISEASES OF THE STOMACH

When clinical, chemical, or roentgenologic evidence suggests the likelihood of a connection between a presenting dermatosis and clinically demonstrable disease of the stomach, local treatment of the skin should be supported by therapy of the gastric disorder. If investigation reveals the presence of acute or chronic gastritis, or of a functional secretory disturbance of the stomach, the case obviously calls for dietary therapy. Tables 62 to 66 present an outline of dietotherapy for acute and chronic gastritis.

In chronic gastritis with hyperchlorhydria the diet is essentially the same as in peptic ulcer. Briefly summarized, the characteristics of such a diet are its high content of protein, with moderate quantities of fat, while the carbohydrates are low. The food should be low in residue, well cooked, and easily digestible. Spices and condiments and alcoholic beverages are strictly excluded. The food should be served at moderate temperatures, either extreme being undesirable. Small and frequent meals are to be given.

TABLE 62.—*Diet in Acute Gastritis*

Purpose of the diet: To reduce the functional activity of the stomach to a minimum by means of a strict diet which can be slowly enlarged as outlined below.

(*1*) *First twenty-four to forty-eight hours:* total restriction of all foods, the patient being confined to bed. Liquids limited to sips of water and weak, unsweetened tea. If need for fluids is urgent, 5 to 10 per cent glucose in saline plus vitamin B complex in adequate amount may be given parenterally.

(*2*) *Third and fourth days:* thin strained gruels made of oats, barley, or rice flour. These are to be prepared with water and egg yolk, and a little butter may be admixed. Moreover, protein milk is usually well tolerated.

(*3*) *Fifth day and thereafter:* gruels prepared with milk; porridges of farina, sago, tapioca, rice, barley, or oats. Then toast, zwieback, vegetable purées, soft cooked eggs, and egg noodles may be successively added as tolerated. Later on meat broth, tender veal or beef, chicken, sweetbreads, lean fish, stewed pears and peaches, and fruit jellies may be included.

The nature of the diet for chronic gastritis with hypochlorhydria or achlorhydria is, in general, the opposite of that for hyperchlorhydria. It is relatively low in protein, moderately rich in fat and carbohydrates, but high in stimulants of the gastric secretion. Fluids should be given in moderation. Foods are prepared in finely chopped or puréed form and

Table 63.—*Diet in Chronic Gastritis with Hyperacidity*

Purpose of the diet: To decrease the secretory and motor activity of the stomach through (1) absorption of the excessively produced hydrochloric acid by foods rich in protein, (2) decreasing the gastric secretion by adequate dietary fat, and (3) use of low residue, nonirritating foodstuffs.

The following foods are prohibited:

Meat extracts
Broths, bouillon, and stock soups
Sausage
Pickled and salted meats
Canned meats

Canned fish

Baked beans
Broccoli, Brussels sprouts, cabbage, sauerkraut
Celery
Corn
Cucumber, pickles
Endive, lettuce
Onions, leeks
Peppers, all types
Tomatoes, all types, except diluted juice
Turnips
All raw vegetables

Fruit juices, except diluted tomato or orange juice
Raw fruits, except ripe banana
Rhubarb

Bran and cereals and breads containing bran
Fresh or hot rolls, bread or muffins

Pastry

Coffee, tea, alcohol
Carbonated beverages

Condiments and seasonings, including catsup, chili sauce, mustard, paprika, pepper, vinegar

All fried foods

Very hot or very cold foods

The following foods are permitted:

Meats, tender, finely chopped
Chicken, minced or chopped
Lean fish

Plain milk, malted milk, milk shake, buttermilk, fermented milk
Cream
Cottage cheese or cream cheese
Butter

Egg in any style except fried; egg custard, eggnog, egg soufflé

Potatoes, boiled, baked, or mashed
Puréed spinach, carrots, peas

Diluted tomato or orange juice
Ripe banana
Apple, well baked and without core or skin
Applesauce

Toasted stale bread, zwieback
Boiled rice, strained oatmeal, farina

Puddings of rice (no raisins), cornstarch, gelatin, tapioca, bread must be thoroughly chewed. Small and frequent feedings are desirable. Strong alcoholic drinks and tobacco should be prohibited if they are causative agents in the production of the lack of gastric acid.

In addition to the diet, appropriate medication is indicated. In chronic gastritis with hyperacidity the modern antacids consisting of the nonabsorbable salts of magnesium and aluminum, such as the trisilicates, phosphates, and hydroxides are useful. These are to be taken immediately following meals in doses of 2 to 4 teaspoonfuls in milk or water.

TABLE 64.—*Sample Menu for Chronic Gastritis with Hyperacidity*

Breakfast: Strained oatmeal with cream and a little sugar
One soft boiled egg
Toast with butter
Milk
Orange juice, diluted with water and served at end of meal

Mid-morning: One glass of milk with zwieback

Lunch: Broiled, finely chopped steak with boiled potatoes, puréed spinach
Toast with butter
Tapioca pudding
Milk

Mid-afternoon: Malted milk shake

Dinner: Cream of potato soup
Minced chicken with macaroni and cheese, puréed carrots
Toast with butter
Sliced ripe banana with cream
Milk

On retiring: Egg custard, one-half glass milk

In chronic gastritis with marked hypo-acidity or anacidity the use of hydrochloric acid plus pepsin is indicated. This may be given in the following prescription:

℞

Dilute hydrochloric acid	15.0	℥ ss
Pepsin	15.0	℥ ss
Distilled water q.s. ad.	180.0	℥ vi

S. 1 tablespoonful in a glass of water through a straw or tube three times daily during meals.

TABLE 65.—*Diet in Chronic Gastritis with Hypochlorhydria, Achlorhydria, or Achylia*

Purpose of the diet: (1) To facilitate digestion of connective tissue in animal foods and cellulose in vegetable foods; (2) to aid digestion of proteins; (3) to stimulate acid gastric secretion.

The following foods are prohibited:

Meats if raw, rare, pickled, or with gristle or fibrous tissue
Sausage containing uncooked meat
Plain milk
Foods with a high bacterial content, such as certain cheeses (e.g., Gorgonzola) and game which has been allowed to become "high"
Raw vegetables, except lettuce
Vegetables with a high cellulose content or which are not readily puréed, such as

cabbage
corn
mushrooms
onions
radish
brussels sprouts
celery
eggplant
okra
peppers
turnips

Raw fruits, except banana
Fruits with a high cellulose content, such as

dates
grapes
figs
raisins

Bread, rolls, and crackers made with bran or from whole grain flour
Alimentary pastes

The following foods are permitted:

Meats, lean, scraped, parboiled (including boiled ham)
Milk diluted with tea, fermented milk such as yoghurt, kefir, buttermilk, lactic acid milk
Cream in small amounts
Mild cheeses with low bacterial content, such as Edam, Swiss, American
Eggs, soft boiled, scrambled, omelets, soufflés
Lettuce
The following vegetables are allowed when thoroughly cooked and puréed:

spinach
asparagus tips
fresh green beans
hearts of artichoke
carrots
cauliflower
fresh peas
mashed potatoes

Ripe banana
Stewed fruits, such as

apples
apricots
strawberries
pears
peaches

Gruels and porridges of all types
Macaroni, noodles, spaghetti
White bread, zwieback, biscuits of white flour
Tea in moderate amounts
Salt and spices in moderate amounts
Light wines and carbonated drinks

Another method of supplying the acid and digestive ferment is the use of glutamic acid hydrochloride in combination with pepsin:

℞

Glutamic acid hydrochloride	0.35	gr. vi
Pepsin	0.40	gr. vii

Misce. Make capsules No. 1. Tales No. LX
S. Two capsules with water three times daily during meals.

Besides the patients having dermatoses based directly upon gastric disease, there are many in whom there is in addition a food hypersensitiveness. In such instances, the treatment outlined above must be supplemented by appropriate antiallergic measures, which are described in some detail in the section on food allergy (p. 256). For example, in a case of urticaria due to hypersensitiveness to beef, dietary treatment of the concurrent gastritis alone could not possibly eradicate the condition, any more than therapy consisting only of administration of Beef Propeptan could be of full benefit. However, strict adherence to the Propeptan routine to combat the allergy combined with the indicated dietary therapy for the gastritis may well result in a complete cure.

Table 66.—*Sample Menu for Chronic Gastritis with Hypochlorhydria, Achlorhydria, or Achylia*

Breakfast: Orange juice
Toasted stale white bread
Unsweetened tea

Mid-morning: Glass of yoghurt or buttermilk
Zwieback

Luncheon: Cup of beef or chicken bouillon
Plain omelet, mashed potato, puréed spinach
Toasted stale white bread
Ripe banana
Unsweetened tea with milk

Mid-afternoon: As for mid-morning

Dinner: Tomato juice
Boiled beef with boiled carrots and peas
Salad of lettuce with small amount of cream cheese
Toasted stale white bread
Stewed pears
Weak, unsweetened tea

On retiring: As for mid-morning

Furthermore, there are cases in which the dermatosis and the gastric disease are concomitant expressions of underlying emotional and nervous states. In these instances the psychosomatic approach plus the use of sedatives often produces excellent responses (Alvarez,[766, 591] Stokes and Pillsbury[734]).

E. DERMATOSES CAUSED BY DISEASES OF THE INTESTINE

In intestinal disorders of different sorts one occasionally encounters such skin manifestations as disseminated dermatitic or urticarial lesions, local or generalized pruritus, and itching papules, often acneiform in character, which appear on the face. These cutaneous lesions are commonly accompanied by such subjective symptoms as fatigue, general malaise, and moderate irritability. It has not yet become possible to determine, in a given case, the precise relationship between the dermatosis and the intestinal disease. Of practical significance, however, are the therapeutic results. In some cases appropriate dietary measures and in others suitable procedures to clear up intestinal infections lead to rapid improvement of the systemic and cutaneous symptoms, which, however, will soon recur if the underlying functional disturbance of the intestines is not permamently controlled.

1. Dermatoses Caused by Diseases of the Small Intestine

The relationship between the diseases of the small intestine, particularly those of inflammatory character, and other tissues, including the skin, is as yet poorly understood. Various theories have been presented, of which two have received some degree of acceptance. The first is based on the possibility of the resorption by the irritated intestinal mucosa of protein cleavage products which would normally have proceeded to complete digestion. The interesting experiments of Gutzeit,[750] described in some detail on page 298, lend support to this hypothesis.

The other theory, which has aroused great interest for decades, is the concept of intestinal autointoxication. This postulates that absorption of toxins naturally present in the intestine, but particularly those produced by a pathologic bacterial flora, produces functional and even organic disturbances elsewhere in the body. Under normal conditions, detoxification of intestinal poisons is accomplished by the mucosa of the bowel and especially by the liver. It is assumed that a breakdown of these lines of defense by disease or by overwhelming amounts of toxin permits the entrance of the latter into the general circulation.

In an excellent review by Alvarez[767] the literature was critically ex-

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[766] Alvarez, W. C.: J. A. M. A. **92**: 1231, 1929.

[767] Alvarez, W. C.: Physiol. Rev. **4**: 352, 1924.

amined and the conclusion drawn that while, from the clinical point of view, there is such a thing as absorption of harmful toxins from the digestive tract, the experimental proof is inadequate and not entirely convincing. Bockus,[768] McLester,[769] and other recent authors take a similar stand.

It is undeniable that there is no conclusive experimental evidence that intestinal autointoxication does occur, but our clinical experience supports the concept that skin diseases can be caused by toxins of intestinal origin. The work of Mutch[738] indicates that resorption of toxins from the digestive tract occurs mainly from the pathologic small intestine but also from the large intestine. Under normal conditions poisons formed in the intestine are detoxified in the liver, to which they are carried by the portal system. However, if the liver is diseased or experimentally by-passed the toxins may enter the general circulation and produce generalized or localized—e.g., cutaneous—symptoms. The work of Magnus-Alsleben[770] serves to illustrate this point. This investigator removed the small intestinal contents of healthy dogs through a fistula and injected this material into rabbits. It was found that injection of a few cubic centimeters into the ear vein regularly killed the animals promptly, but that injection of the same quantity into the portal vein was not fatal. This experiment clearly demonstrates that the contents of the small intestine normally contain some toxic substances which are detoxified in the liver. It is also interesting to note Magnus-Alsleben's observation that the toxic action of the contents of the small intestine was greater when the animals were on a meat or a mixed diet.

In man it is obviously not feasible to carry out experiments such as have been made in animals. We are therefore entirely dependent upon clinical observation.

Mutch[738] has demonstrated that, in man, toxic substances may be produced by intestinal stasis with consequent absorption of by-products of bacterial action from the small intestine. He also states that the toxicity can be increased by a diet too rich in proteins. Barber,[179] while admitting that the term "intestinal toxemia" has been used too frequently as a cloak for ignorance, is of the opinion that, apart from cases in which the toxins of definitely pathogenic bacteria are absorbed and escape destruction in the liver, excessive bacterial growth and activity in the small intestine, rather than in the colon, is of great importance in engendering absorption of toxic substances, provoking thereby skin manifestations. Too rapid passage of the contents of the small and large intestines, re-

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[768] Bockus, H. L.: Gastroenterology. Philadelphia: Saunders, 1944. 2nd ed.

[769] McLester, J. S.: Nutrition and Diet in Health and Disease. Philadelphia: Saunders, 1943.

[770] Magnus-Alsleben, E.: Beitr. chem. Path. **6**: 503, 1906.

sulting in unformed and semiliquid stools, constitutes another factor leading to intestinal intoxication through carrying into lower segments of the intestinal tract materials which do not normally belong there and upon which the bacterial flora may act abnormally. This acceleration may be due to any of a number of causes, such as enteritis, colitis, use of irritant purgatives.

The nature of the toxic substances responsible for the cutaneous symptoms may unquestionably differ from case to case. They may be derived directly from intestinal bacteria or from the action of bacteria upon undigested food. According to Becher,[771] we are now relatively well informed as to the nature of these intestinal toxins, the most important of which are skatol, indol, phenol, coproporphyrin, and certain fatty acids. Some students of this question are inclined to believe that intestinal intoxication is attributable to increased histamine formation; and some French authorities, notably Loeper, Bioy, and Perrault, go so far as to state that imidazolemia is an important cause of urticaria and angioneurotic edema. However, all that can be said is that our present information on this question is sadly inadequate, largely owing to the fact that we are not in a position to determine just how much histamine is formed and resorbed in the intestinal tract. The presence of histamine in the intestine is in itself in no way pathologic. Although highly toxic when administered parenterally, its action is very slight when it is resorbed from the intestine (Koessler and Hanke[772]). On the other hand, Lieb[773] claims to have achieved good therapeutic results in a number of conditions, including urticaria and chronic dermatitis, with measures designed to prevent excessive histamine formation, a procedure which he terms "dehistaminization."

Lastly, it should be recalled that damage to the intestinal wall due to enteritis or ulcus can pave the way for allergization by some food which may, in turn, produce allergic dermatoses.

Enteritis is most commonly caused by overtaxing the alimentary tract either by consumption of large amounts of relatively undigestible foods or as the result of inadequate gastric function even on an easily digestible dietary.

Aside from the usual symptoms and signs, which are not within the province of this volume, microscopic examination of the stool is often a valuable aid in the diagnosis of enteritis. It is characterized by the presence of increased amounts of soaps, generally in the form of crystals and flakes, less commonly in the form of droplets, and needle-like fatty

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771. Becher, E.: Klin. Wchnschr. **16:** 145, 1937.
772. Koessler, K. K. and Hanke, M. T.: J. Biol. Chem. **59:** 803, 1924.
773. Lieb, C. W.: New York State J. Med. **24:** 295, 1924.

acid crystals. For this purpose the patient should be kept on a relatively fat-free diet for a few days prior to examination of the stool. However, it is important to rule out conditions presenting similar stool pictures, such as icterus, secretory disturbances of the pancreas, and obstruction of the thoracic duct. Another valuable diagnostic procedure in enteritis is roentgenologic examination, which may reveal hypermotility of the small intestine of such a degree that some of the barium reaches the large intestine as early as two hours after ingestion of the contrast meal.

Enteritis is occasionally the cause of chronic, therapy-resistant cases of dermatitis, urticaria, and lichen urticatus (see Figs. 104, 105, 106).

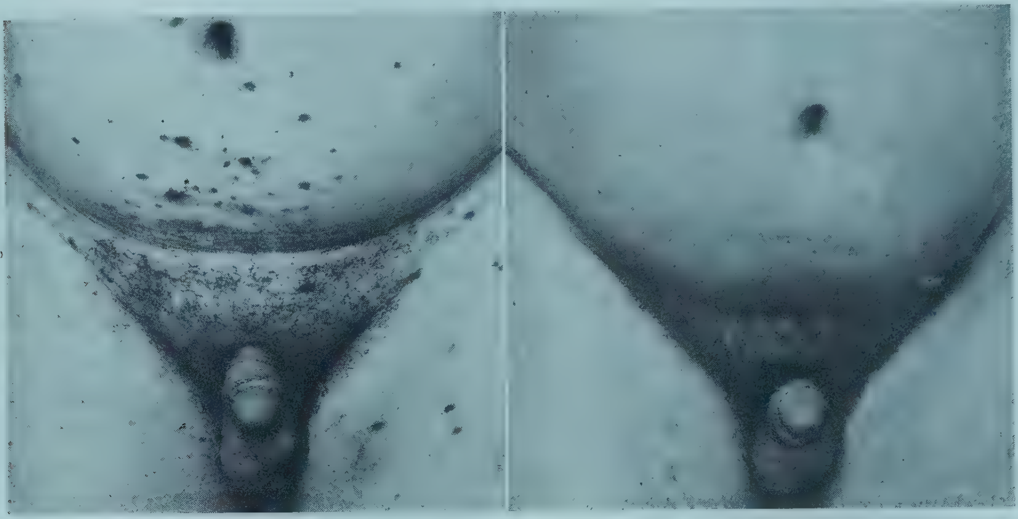

Fig. 104 Fig. 105

Lichen Urticatus on the Basis of Chronic Enteritis

Fig. 104. This 34 year old man suffered for two years from a therapy-resistant, intensely pruritic dermatosis following a strict obesity diet which contained a high proportion of cellulose. Diagnosis of enteritis was finally made.

Fig. 105. The patient was cured without local measures, by means of a diet very low in cellulose but rich in milk (2 liters a day). Case was observed for two years without recurrence of cutaneous lesions.

2. Dermatoses Caused by Diseases of the Large Intestine

In the large intestine, fermentation and putrefaction are the principal factors in the production of intestinal toxins. Moreover, colopathies such as spastic or irritable colon, often associated with mucous colitis, may give rise to intestinal toxemia and consequently to dermal lesions (Friedenwald and Morrison[735]). Chronic constipation may also play a role. The precise nature of the toxins produced in the colon is as yet unknown. Nor has it been determined whether their action upon the skin in producing dermatoses or pruritus is a direct result of their resorption from the intestinal tract or an indirect effect through heightened cutaneous susceptibility. Another possibility is that the toxic substances produced in the colon pass into the liver and then act as harmful products, as suggested by Smithies.[774] None of these hypotheses has thus far received experimental confirmation.

The proponents of the concept of intestinal autointoxication rely heavily upon the presence of increased amounts of indican in the urine or blood. In this connection it may be well to recall Alvarez's[767] criticism that such findings are of limited value, since increased amounts of indoxyl sulfates and ethereal sulfates in the urine may also occur in other conditions. Therefore, much of the literature concerning the etiologic significance of intestinal autointoxication in a great variety of dermatoses (for bibliography, see Lutz[276]) must be re-evaluated in the light of our present views on the subject. Nevertheless, time and again the physician has occasion to observe in his daily practice that there definitely is a causal relationship

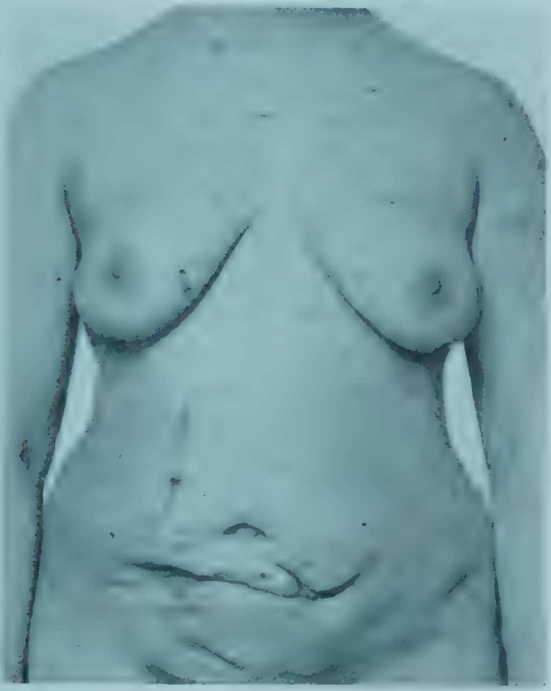

Fig. 106. Lichen Urticatus on the Basis of Chronic Enteritis

A 36 year old woman with severe pruritus and lichen urticatus of more than ten years' duration. Because of constant pain in the upper abdomen, cholecystectomy was performed, without improvement of the symptoms. Appendectomy similarly failed to give relief. Diagnosis of enteritis was established by stool examination. As long as the patient adhered to a strict enteritis diet (see text) the cutaneous and gastrointestinal symptoms were alleviated without local therapy.

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[774] Smithies, F.: Ann. Int. Med. 3: 1201, 1930.

between intestinal disorders and the appearance and disappearance of cutaneous diseases. Although we are rarely able to identify the toxic substance chemically, it is nevertheless occasionally possible to do so. Thus van den Bergh[775] succeeded in proving that the bluish discoloration of the skin and mucous membranes occurring in "enterogenous cyanosis" is due to methemoglobin and sulfhemoglobin produced by intestinal putrefaction in the bowel and appearing in the blood. This disease is due to almost complete intestinal obstruction, sometimes persisting for years, and is accompanied by systemic symptoms of intoxication which disappear completely following adherence to a strict milk diet. These cases meet all the criteria needed to determine that a presenting condition is due to an underlying intestinal intoxication.

For a discussion of other ways in which intestinal autointoxication can be brought about, the reader is referred to the preceding section (page 307).

There are three chief causes for the production of toxins in the large intestine, namely, putrefaction, fermentation, and constipation. A brief discussion of the diagnostic characteristics and the dietotherapy of these conditions is desirable.

The two principal forms of intestinal dyspepsia which lead to intestinal autointoxication are the putrefactive and the fermentative types. The diagnosis of these conditions depends largely on the macroscopic and microscopic examination of the stool—a procedure which can be done by the physician in his office. It is essential that, for three days prior to the stool examination, the patient be kept on a special diet, such as that outlined by Schmidt. This diet is made up of foods so selected and prepared as to be readily digestible by a normal intestine. This makes it possible to determine whether food residues in the feces are normal. The Schmidt test diet is rich in carbohydrate and fat and contains raw meat. Therefore, examination of the stool will disclose any impairment of the ability to digest protein, carbohydrate, or fat (Table 67).

The character of the stool, its color and odor, the presence of mucus, blood, undigested food particles give valuable information. In putrefactive dyspepsia there is an exceedingly foul-smelling, alkaline, dark brown stool which suggests proteolytic decomposition. Under the microscope are seen undigested connective tissue and various kinds of poorly digested food particles. However, blood and mucus are not present. In fermentative dyspepsia the stool presents a characteristic and unmistakable appearance. The feces are abundant, light in color, acid to litmus, and have a sour odor and bubbles of gas indicating abnormal fermentative activity. Microscopically the most important features are undigested starch and an iodophilic bacterial flora.

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[775] VAN DEN BERGH, H.: Arch. f. klin. Med. **83:** 86, 1905; Berl. klin. Wchnschr. **43:** 7, 1906.

It is not always easy to distinguish between putrefactive and fermentative states. The presence of connective tissue fragments points to some disturbance of gastric digestion; muscle fibers with recognizable striation suggest pancreatic insufficiency. Sago-like granules of potato indicate poor digestion of starch.

It is to be noted, however, that for proper interpretation of the stool following the Schmidt test diet considerable experience is necessary. The reader is referred to Bockus[768] for microscopic pictures of representative stools.

In the management of putrefactive and fermentative states it should be borne in mind that these conditions may be concurrent, the picture being dominated first by the one and then by the other. In cases of this kind, dietary treatment must be adjusted accordingly.

Fermentative intestinal processes are encountered in a variety of skin diseases, such as dermatitis, rosacea, and pruritus ani. In dealing with these conditions, the physician should not prescribe a vegetarian diet indiscriminately; and if such a diet is given, the patient must be kept under close observation. While a vegetable regimen enhances the detoxifying function of the liver, this form of diet may not be well tolerated. When continued too long, it is likely to lead to intestinal dysbacteria (Roux and Goiffon), or to a disturbance of the acid-base balance of the digestive secretions with consequent repercussions in the skin (Desaux and Antoine[736]).

TABLE 67.—*Schmidt Test Diet*

Purpose of the diet: To provide a standard dietary for a three day period in order to determine, by examination of the stool, the digestive capacity of the gastrointestinal tract for protein, carbohydrate, and fat.

Breakfast: 500 cc. of milk with 50 Gm. of zwieback
Mid-morning: Oatmeal gruel (40 Gm. of rolled oats, 10 Gm. of butter, 200 cc. of milk, 300 cc. of water, and one egg, salted to taste)
Luncheon: 125 Gm. (raw weight) of finely chopped beef lightly broiled, so that the interior remains uncooked; in addition, potato purée made of 200 Gm. of potato, 100 cc. of milk, and 10 Gm. of butter, salted to taste
Mid-afternoon: Same as for breakfast
Dinner: Same as mid-morning

In this connection it is interesting to note the recent investigations of Ottenstein and Ethem,[776] who report that increased acid formation in the intestine due to putrefactive processes seems to be an etiologic factor in the pathogenesis of skin diseases. The indican absorbed from the in-

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776. OTTENSTEIN, B., and ETHEM, R.: Dermatologica 81: 170, 1940.

testine is generally detoxified in the liver and eliminated by way of the kidneys. Pathologic processes in various organs, notably in the liver or kidneys, may impair indican excretion. As a result, the indican level in the blood is increased, thereby predisposing the skin to various diseases. Ottenstein recommends, therefore, that in cases with intestinal putrefaction the indican level as well as the alkaline reserve of the blood be determined.

It should be stressed, however, that cutaneous manifestations may be due not only to fermentative and putrefactive processes and their resultant toxins, but also to inflammatory processes in the colon. These latter conditions include, notably, inflammation of the cecum and the adjacent colon. This may be caused by the accumulation of feces in the cecum as a result of a high residue diet, or faulty digestion in the stomach and small intestine resulting in the accumulation of large amounts of incompletely digested food, and last but not least by constipation.

Particularly in achylia, which is not infrequently associated with dermatitis, incompletely digested food reaches the cecum and irritates the mucosa, ultimately provoking an inflammatory reaction. Because of this, examination of the urine for putrefactive products may show a strongly positive indican test and, furthermore, a very pronounced Millon reaction, particularly in the presence of constipation. However, these manifestations are not always due to absorption of the products of putrefaction of the intestinal chyme or to simple constipation; they can also be due to putrefaction of the protein of the excessively produced mucus and secretions of the intestine.

The sequence is as follows: First, repeated irritation of the mucosa of the cecum and the adjacent colon leads to inflammation of the cecum and the first portion of the transverse colon. This induces hypersecretion, which stagnates in the cecum and becomes putrescent. The putrefactive products cause additional irritation of the intestinal mucous membrane which, in turn, produces an excess of mucus; the chyme, entering the colon from the small intestine, becomes infected with a multitude of putrefactive bacteria, with the result that normal fermentation is inhibited and abnormal putrefaction of the chyme sets in. Absorption of these putrefactive materials seems to be the primary cause of some cases of pruritus, dermatitis, urticaria and lichen urticatus (Figs. 107, 108). Thus, Porges[777] and the writer have observed instances in which both the intestinal disorder and the cutaneous manifestations yielded promptly to dietary therapy plus appropriate topical measures, with recurrence of the symptoms when the dietary regimen was discontinued. The management of cecitis with diet is very similar to that of putrefactive dyspepsia (see p. 320).

[777] Porges, O.: Wien. klin. Wchnschr. 39: 566, 1926.

The exact identity of the causal putrefactive products has not as yet been determined. It must be stressed, furthermore, that a putrefactive state does not necessarily provoke cutaneous symptoms, probably because not all these products are capable of irritating the skin. A more likely explanation is that the degree of cutaneous susceptibility to such influences probably varies considerably from one individual to another. Porges[777] is of the opinion that the skin of neurasthenic individuals and those with vasomotor instability is likely to be especially susceptible.

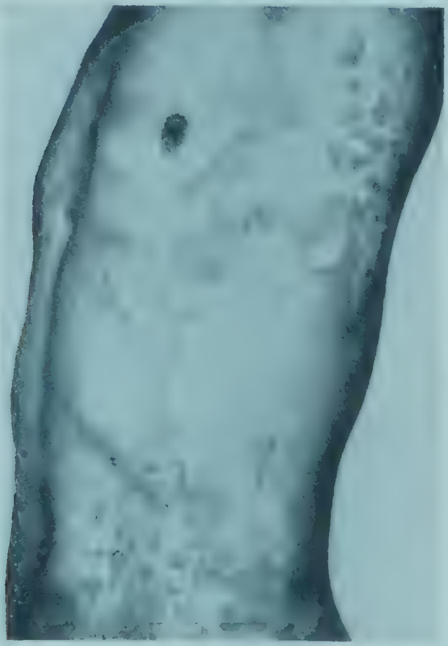

FIG. 107. URTICARIA ON THE BASIS OF INTESTINAL PUTREFACTIVE DYSPEPSIA

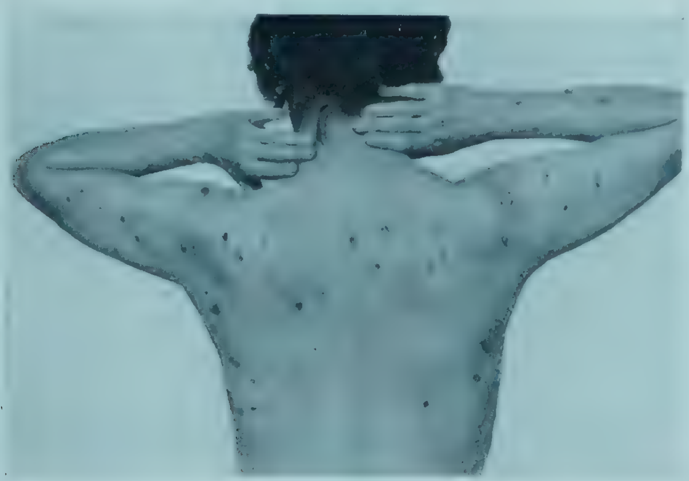

FIG. 108. LICHEN URTICATUS DUE TO INTESTINAL PUTREFACTIVE DYSPEPSIA

Irritability of the colon and mucous colitis, which are generally neurogenic in origin although often the result of irritation either in the gastrointestinal tract or in the adjacent organs (McGavran[778]), are quite commonly accompanied by cutaneous manifestations. Thus, in a series of fifty cases, Bockus and his associates[779] found that 30 per cent of their patients gave histories of urticaria or angioneurotic edema. These authors believe that the cutaneous manifestations associated with such intestinal conditions are due to a labile, cutaneous-vasomotor background, as evidenced by such additional symptoms as hot flashes, cold hands and feet, itching, blotchy areas on the skin, and dermographism. Mention must also be made here of cases reported by Ramel,[780] in which idiopathic ulcerative colitis was accompanied by disseminated ulcerative-necrotic lesions, on the extremities and in the inguinal folds, which were reminiscent of papulonecrotic tuberculids. Histologic examination revealed circumscribed necrosis of the cutaneous end arteries analogous to the processes in the intestinal mucosa. Felsen[781] reported three patients in whom multiple necrotizing skin lesions first manifested themselves during an exacerbation of chronic ulcerative colitis.

Dermatoses are less commonly caused by inflammatory processes in the appendix. Ehrmann[782] describes a case of neurodermatitis which cleared up following surgical removal of a chronically inflamed appendix; and also a case of chronic dermatitis associated with stenosis of the vermiform appendix due to tuberculosis, in which the cutaneous condition disappeared and remained absent for two years, following appendectomy, only to reappear when the intestinal tuberculosis recurred. Leriche[563] observed two cases of urticaria due to meat, in which removal of the inflamed appendix served to eradicate the allergic hypersensitiveness.

Whitfield[783] applied the term "dermatitis colonica" to a rather indefinite eruption similar to parapsoriasis. The borders of the patches show fairly discrete red macules without noticeable alteration of the texture of the skin. Inspection with a hand lens reveals well defined telangiectases in these lesions. This disease is associated with a great predominance of varieties of streptococcus in the stool, sometimes with complete absence of Bacillus coli. The condition yields to intestinal antiseptics, a readily digestible diet, and regularity in meals.

It may be pertinent at this point to call attention to a certain degree of interdependence between intestinal disease and pathologic pigmentation

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778. McGavran, C. W.: J. A. M. A. **120:** 182, 1942.
779. Bockus, H. L., Bank, J., and Wilkinson, S. A.: Am. J. M. Sc. **176:** 813, 1928.
780. Ramel, E.: Bull. Soc. franc. de dermat. et Syph. **42:** 608, 1935.
781. Felsen, J.: New York State J. Med. **41:** 2228, 1941.
782. Ehrmann, S.: Arch. f. Dermat. u. Syph. **87:** 438, 1907.
783. Whitfield, A.: Brit. J. Dermat. **44:** 24, 1932.

of the skin, as seen clinically in the form of chloasma. It is probable that oxidation of certain substances of the aromatic group, structurally similar to phenol and possibly also to skatol, leads to melanosis.

Turning now to chronic constipation, the question arises as to how this condition may be related to the etiology of certain skin diseases. Chronic constipation can induce an abnormal bacterial flora in the small intestine, which in turn may promote pathologic decomposition of the products of proteolysis. This is due in part to the reverse peristalsis which, according to Alvarez,[784] results from slowing or stoppage of the downward fecal current. Thus, Mutch[738] cultivated pathogenic bacteria from the duodenal contents in patients with constipation.

The principal causes of chronic and habitual constipation may be divided into three groups: (1) alimentary constipation produced by a diet lacking the necessary bulk and roughage to promote adequate peristalsis in the large intestine; (2) atonic constipation resulting from a subnormal peristaltic response on the part of the intestine to an adequate supply of roughage (subnormal excitability of the intestinal nervous mechanism); (3) spastic constipation, in which more or less extensive segments of the large intestine are in a spastic state, with the result that the stool is passed in thin form or as small scybala.

Lastly, the role of intestinal flora will have to be accorded far more consideration than it has received to date. Bacteriologic examination of freshly passed stool shows, under physiologic conditions, an overwhelming majority of so-called normal B. coli and relatively few enterococci. Different conditions prevail in the higher segments of the intestine, the contents of which can be examined only by means of intestinal intubation and, therefore, are not carried out as an ordinary clinical procedure. As Hoering[785] and others have demonstrated, under pathologic conditions one encounters in the large intestine a wide range of bacterial pathogenicity, from normal strongly acid-forming B. coli to alkaline-producing B. paracoli. In chronic disturbances of the stomach and small intestine B. coli often acquires the ability to act hemolytically and thus may play a role in producing anemia. Pathologic flora in the enteric canal may also include hemolytic streptococcus, Streptococcus viridans, hemolytic staphylococcus, Bacillus proteus vulgaris, fungi, yeast, and gram-positive bacilli. As our own experience has shown us, in addition to the aerobic flora we must pay special attention to the anaerobic flora as well. Notably, Clostridium welchii and Bacteroids are of importance in this respect.

In this connection it may be mentioned that the writer's own studies

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784. ALVAREZ, W. C.: J. A. M. A. **69:** 2018, 1917.
785. HOERING, F. O.: Klin. Wchnschr. **15:** 697, 195.

have revealed that in the intestine pathologic gram-positive flora or hemolytic B. coli are apparently capable of producing porphyrins which, in turn, can promote light sensitization of the skin. Since these cases regularly also present signs of hepatic damage which may be of considerable practical importance, the subject will be considered in further detail in the section on the liver (p. 337).

To all appearances, intestinal bacteria play an important role in the nutrition of man and of animals. Thus, biotin, one of the vitamins of the B complex, is supplied in man in greater quantities by intestinal bacteria than by the diet itself (Oppel[785a]). On the other hand, as Elvehjem[18] has pointed out, nutrients, particularly vitamins, have an important biologic effect upon the bacterial flora of the intestinal tract. They stimulate the growth of certain micro-organisms, and the latter, in turn, have the capacity of synthesizing other vitamins and nutrients.

Under normal conditions the bactericidal action of the hydrochloric acid produced in the stomach regulates the gastric and thus also the intestinal flora arising as a result of ingestion of foods containing bacteria. This is not the case, however, in anacidity and hypo-acidity. As Hoering[785] has demonstrated, these conditions favor the development of abnormal hemolytic powers on the part of B. coli and the cocci and, indeed, alter the entire fecal flora.

Pathologic intestinal micro-organisms may reach the skin via the blood stream or the lymphatics and cause cutaneous abscess formation. Desaux and Rabeau found intestinal bacteria in pus in the lesions of a case of hidradenitis and cured the condition by administering the appropriate vaccine. In an instance of recurrent furunculosis reported by Antoni, the patient's intestinal flora was found to consist almost exclusively of Staphylococcus aureus. The present writer observed a case of severe, persistent furunculosis which yielded only to systemic oral administration of Mutaflor, a preparation of viable B. coli. Moreover, we have had the opportunity of seeing the following striking case:

A woman, aged 33, had for some years been suffering from frequently recurring abscesses of the skin of the lower abdominal region and on the anterior aspect of the thigh (Fig. 109). Cultures from these lesions invariably revealed pure strains of B. coli. The intracutaneous test with B. coli vaccine was strongly positive.

In other cases, the intestinal bacteria may reach the skin by direct contact and multiply there. This is due in some instances to bacteria making their way from open wounds, such as postoperative intestinal fistulae, to the adjacent skin, where they produce gangrene (Jausion) or phagedenic ulcerative lesions (Halkin, Ramel). In other cases, the bacilli take the hematogenous route, as in B. coli bacillemia, and lead to a kind of roseola abdominalis, similar to that of typhoid (Constanzi), or, far more commonly, to erythema, urticaria, or dermatitis. According to H. and J. Montlaur,[786] a special role is played by enterococci in infants. Under normal conditions, the enterococcus is essentially saprophytic in character, both in the intestine and on the skin. Occasionally, however, this organism seems to act as excitant in certain skin diseases, notably in infants and small children, particularly in a dermatitis of the buttocks which develops between the ninth and the fortieth day after birth. Complete cure not only of the skin condition, but also of the associated digestive disturbance, is effected by enforcement of a suitable diet and administration of an antienterococcus vaccine (Criou[787]).

[785a] Oppel, T. W.: Am. J. M. Sc. **204**: 856, 1942.

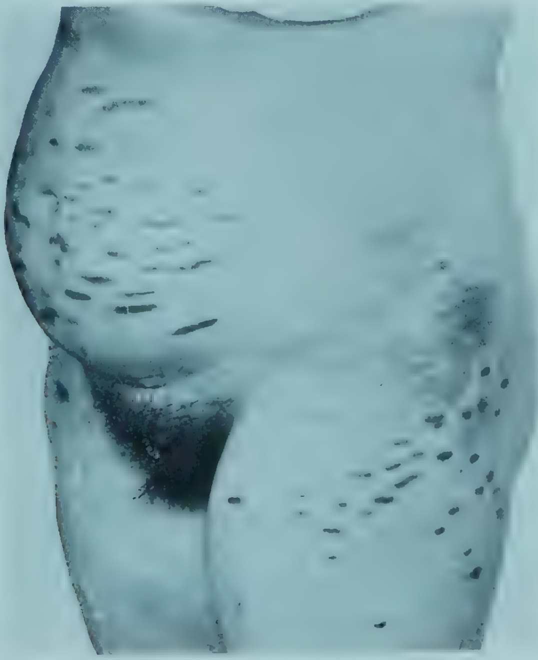

Fig. 109. Multiple Abscesses of the Skin Due to B. coli Infection

3. Dermatoses Caused by Diseases of the Rectum

Almost every proctitis, whether produced by infection or by some other pathologic cause in the colon, is accompanied by anal dermatitis or pruritus, conditions which are most unlikely to respond to local treatment until the underlying process is controlled. The dermatitis and the itching are the result of constant irritation by the intestinal secretions.

Rectal fistulas often bring about perianal dermatitis as the result of the continual moistening of the skin. Furthermore, erosions and rhagades of the rectal mucosa can also lead to dermatitis of the surrounding skin areas, notably when the patient cannot refrain from scratching the perianal zone. In all cases of this kind, the only effective therapeutic approach is one that takes due consideration of the rectal condition itself. In dealing with anal dermatitis and/or anal pruritus, the possibility of intestinal parasites, particularly of oxyuris, must always be borne in mind. Lastly, in occasional cases food allergy may be the underlying cause (see page 441).

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[786] Montlaur, J. H.: Nutrition 6: 139, 1936.

[787] Criou, P.: Thèse de Paris 18: 146, 1933.

F. INTESTINAL DISTURBANCES DUE TO SKIN DISEASES

The possibility of this particular interrelationship has been virtually overlooked to date. In the literature, the writer has encountered only Puntoni's report[754] of his interesting experimental work, in which application of a coat of varnish to the skin of an animal caused anatomically demonstrable damage to the intestine (loss of epithelium). These lesions are accompanied, furthermore, by certain modifications of the normal intestinal flora, notably by increased virulence of B. coli. At the same time, the intestinal walls of such animals become abnormally permeable not only to the micro-organisms of the normal intestinal flora but particularly to pathogenic bacteria when the latter are artificially introduced into the intestine. This heightened permeability is attributable to a reduction of the bactericidal power of the blood of varnished animals.

G. CUTANEOUS AND INTESTINAL DISTURBANCES AS CONCOMITANT EXPRESSIONS OF AN UNDERLYING DISEASE

One commonly encounters a picture of cutaneous and intestinal disturbances in which it is impossible to demonstrate an interdependence between the concurrent conditions. In cases of this kind, one must always envisage the possibility that both the cutaneous and the intestinal symptoms may be due to some underlying humoral or neuro-endocrine imbalance, or that the skin and the alimentary tract may have been similarly affected by some intoxication or infection, and that both organs are thus simultaneously engaged in eliminating the toxic substances. Symptoms of hypersensitiveness can manifest themselves at the same time in the skin and in the mucous membranes of the internal organs.

H. THERAPY OF DERMATOSES DUE TO DISEASES OF THE INTESTINE

The treatment of dermatoses in which there is presumptive evidence of an intestinal etiology depends upon the type of the intestinal disease.

Table 68 presents a summary of the dietary treatment of chronic enteritis.

Tables 69 and 70 present the dietary treatment of fermentative and putrefactive dyspepsia.

If there is constipation, it is essential to learn its cause by means of radiographic study of the intestinal tract. It is important to ascertain whether the constipation is atonic or spastic or due to some organic cause such as diverticulitis in order to institute appropriate dietary therapy (Tables 71–74). Moreover, the location of the delay should be determined, whether in the lower ileum, the cecum, or the colon. Finally, it is important to know whether gastritis is present and if the gastric secretion is normal. In the presence of abnormal phenol and indican excretion in the urine or a high indican level in the blood, findings sometimes considered as indicative of intestinal autointoxication, or if there is a pathologic intestinal flora, the most effective therapeutic approach is likely to be that which attempts to reduce to a minimum the formation of toxins in the intestine. This is best achieved by means of a lactovegetarian diet, since the casein of milk is less subject to putrefaction than are the proteins of meat or eggs. Gelatin is especially valuable, since it contains no aromatic amino acids and therefore produces no strong toxins. Needless

TABLE 68.—*Diet in Chronic Enteritis*

Purpose of the diet: To facilitate digestion of cellulose in vegetable foods and of connective tissue in animal foods.

The following foods are prohibited:

Fat, tough, pickled, or spiced meats
Fat, smoked, or pickled fish
All vegetables, including the legumes, but excepting potatoes
All fruits, raw or cooked, except fruit juices
Preserves, jellies, and marmalades
Rye bread, pumpernickel, bread made from whole grains
Spices, condiments
Tea, coffee

The following foods are permitted:

Tender, lean meat, fish or fowl, thoroughly cooked
Milk
Potato purée
White bread
Well cooked rice, cream of wheat, sago
Noodles, macaroni, spaghetti
Vegetable juices
Fruit juices

TABLE 69.—*Diet in Putrefactive Dyspepsia*

Purpose of the diet: (1) To restrict proteins, which provide a fertile soil for bacterial growth and putrefaction in the small and large intestines; (2) to correct gastric hypo-acidity and hypermotility, which frequently promote putrefactive dyspepsia; and (3) to reduce the secretion of the succus entericus, which is naturally rich in protein and therefore readily subject to putrefaction; this is accomplished by means of a nonirritating, low cellulose diet.

Procedure:

First and second days—10 per cent solution of table sugar in boiled water; 80 to 100 Gm. (2.5 to 3 oz.) of sugar, total for the day.

Third day—15 per cent solution of table sugar in boiled water; 200 Gm. (6 oz.) of sugar, total for the day.

Fourth day and thereafter—the diet is increased progressively as tolerated. The following foods are permitted (listed approximately in the order in which they should be added to the diet):

Gruels and porridges made from flour or farina. Cereals prepared for infant use are of value. These should be liberally enriched with butter.

Sour milk, buttermilk, and yoghurt are very useful. Fresh milk is poorly tolerated.

Fresh cottage cheese.

Gelatin preparations, soft boiled or scrambled eggs.

Meats, very tender, finely ground, and thoroughly cooked.

For some months thereafter the patient is to avoid all foods containing large amounts of cellulose (the coarser vegetables), fibrous material (tough meats), and highly spiced or well seasoned foods (sausage).

TABLE 70.—*Diet in Fermentative Dyspepsia*

Purpose of the diet: To correct excessive fermentation in the bowel by elimination or restriction of foods with a high cellulose and carbohydrate content for a limited time.

First two days: Moderately strong meat broths with egg yolk, fresh cottage cheese (with cinnamon if desired), tea without cream or sugar. These are to be served in small portions every two hours.

Third to seventh day: Add protein milk, eggs, Swiss or American cheese, bouillon with beef marrow.

Second week and thereafter: Cautiously add sugar and thin gruels in gradually increasing amounts. Then bread and rolls made from sifted, fine wheat flour are allowed. Thereafter, small amounts of tender, well cooked meats and potato purée are added to the diet. The addition of vegetables and fruits is the next step and begins with tender, thoroughly cooked puréed vegetables and with fruit juices. Raw fruits and vegetables are offered at the very last.

Many patients who have had fermentative dyspepsia must avoid for an indefinite period such foods as the cabbage family, coarse breads, and sour wines. A recurrence of symptoms can be readily controlled by fasting for one or two days.

to say, the organism's requirements in protein cannot be met with gelatin alone; but the balance can be made up with small quantities of other proteins in the form of milk products and particularly of nuts. A diet of this kind serves to restrict intestinal putrefaction considerably. Furthermore, the use of adsorbents, such as animal charcoal or kaolin, appreciably reduces the resorption of intestinal toxins by binding them without diminishing the bactericidal capacity of the small intestine.

TABLE 71.—*Diet in Spastic Constipation*

Purpose of the diet: To avoid foods with a high content of cellulose in order to decrease the irritability of the colon.

The following foods are prohibited:

Apples
Berries
Dates
Figs
Grapes
Melons
Peaches
Pears
Plums
Pomegranate
Prunes
Raisins
Rhubarb

Asparagus
Beans
Peas
Lentils
Beets
Cabbage
Cauliflower
Celery
Corn
Eggplant
Okra
Onion
Parsnips
Sweet peppers
Pumpkin
Radishes
Squash
Spinach

Bran
Whole grain cereals
Whole grain breadstuffs

Nuts

The following foods are permitted:

Tender meats, chicken and fish
Eggs
Milk
Cheese
Butter, cream and oils
White potatoes
Strained soups
Puréed vegetables and fruits
Vegetable and fruit juices

Alimentary pastes
Arrowroot flour products
Crackers and biscuits made of refined flour
White bread
Zwieback
Refined cereals
Gruels
Ice cream and sherbets
Sugar, honey, molasses
Jellies
Starches
Gelatin
Sago

TABLE 72.—*Sample Menu for Diet in Spastic Constipation*

First 7 to 10 days:

Breakfast:	Strained fruit juice Cereal gruel with milk or cream and sugar Milk, or coffee with cream and sugar
Mid-Morning:	Eggnog or yoghurt
Luncheon:	Strained soup White bread or zwieback with butter and honey Purée of stewed apples Milk or buttermilk
Mid-afternoon:	Malted milk or junket
Dinner:	Strained or cream soup Lightly scrambled or soft boiled eggs White bread or zwieback with butter or cream cheese Sherbet or gelatin Plain or malted milk
On retiring:	Warm milk

Thereafter gradually add puréed vegetables, puréed fruits, tender minced meats or fish.

TABLE 73.—*Diet in Atonic Constipation*

Purpose of the Diet: To increase the amount of roughage in the food, filling the bowel with bulk and thus providing a stimulus to peristalsis.

The following foods are prohibited:

Cheese
Fried foods
Puréed foods
Potatoes
White bread
Foods low in physical bulk

The following foods are permitted:

Meat, fish, fowl in moderate quantities
Eggs
Milk
Whole grain cereals and their products
Vegetables, cooked or raw, not puréed; no potatoes
Fruits, cooked or raw, not puréed
Honey

Another approach consists of attempting to suppress the putrefactive agents in the intestine by means of acid-forming foods. Of these, the most widely used are Bacillus acidophilus cultures in various forms, which unquestionably achieve practical results when fresh preparations are taken together with lactose. In the writer's experience, whey cultures of Bacillus acidophilus used in this manner have given gratifying results. By this method there is implanted in the colon a fermentative organism which displaces putrefactive bacteria, thereby decreasing the toxicity of the colonic flora. A somewhat less effective method is the use of yoghurt. Contrary to common belief, yoghurt does not establish colonies of lactic-acid-forming micro-organisms in the intestine; its good effects are due to its lactose content, which reaches the lower segments of the intestinal tract and there militates against putrefactive processes.

TABLE 74.—*Sample Menu for Atonic Constipation*

Breakfast:	Canteloupe Cooked or prepared whole grain cereal with cream and sugar Poached eggs Whole wheat toast with butter Milk, or coffee with cream and sugar
Luncheon:	Meat or fish Whole kernel corn, lettuce with dressing Bran muffins with butter Sliced peaches Milk, or coffee with cream and sugar
Dinner:	Meat or fish Cauliflower with butter; beet salad Pumpernickel with butter Fruit compote Milk, or tea with sugar

Attempts have been made to suppress the pathologic intestinal flora by introducing viable and vigorous strains of B. coli, as contained in the preparation Mutaflor. This method, introduced by Nissle,[571] was of definite value in many of the present author's cases.[788]

In severe cases, a period of fasting may be worth trying. It has been demonstrated that total abstinence from all foods leads to a very marked decline in the number of bacteria in the stool and, in addition, stimulates the excretory functions of the intestine, thus accelerating the elimination

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788. URBACH, E.: Klin. Wchnschr. 17: 304, 1938.

of intestinal toxins. Before instituting the fast, it is advisable to purge the intestine thoroughly, preferably with castor oil or magnesium sulfate.

Disinfectant medication may also serve to reduce the number of intestinal bacteria and thereby decrease intestinal toxins. Disinfectants such as sodium ricinoleate and creosote carbonate (0.1 Gm. in gelatin capsules, three times a day) are frequently effective.

The present writer has also tried chemotherapy, using succinylsulfathiazole. However, in conformity with Behrend's findings,[789] he has observed that while this drug most notably inhibits the B. coli group of bacteria, the number of streptococci actually increases. This is the opposite of the desired therapeutic effect.

Lastly, diseased tonsils, teeth, and other foci of infection such as the gallbladder should be removed. Intestinal bacteria are also encountered in great abundance on the human skin. Every effort should be made to keep the skin clean as a precaution against cutaneous infection by such micro-organisms. This is especially important in connection with child care. For example, a mother suffering from intestinal dysbacteria can readily inoculate the gastrointestinal tract of her nursing infant with abnormal intestinal flora (Becher[771]) which may be instrumental in cutaneous manifestations in the child.

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789. Behrend, M.: J. A. M. A. **128:** 9, 1945.

CHAPTER VII

Dermatoses Due to Diseases of Liver and Pancreas

ALTHOUGH the many functions of the liver have not as yet been fully explored and understood, even our present rather meager knowledge indicates that their relationship to diseases of the skin is of considerable importance.

Among the more important functions of the liver are the metabolism of protein, carbohydrates, and fat; the metabolism of certain vitamins (e.g., conversion of carotene into vitamin A); phosphorylation and other enzymatic processes; the regulation of the water balance; the formation and processing of the bile and its various components; and certain excretory, detoxifying, and antiallergic activities. It is well established that, aside from its participation in the digestive and absorptive processes in the small intestine, the liver has a most important role in the utilization of food and that functional hepatic disturbances or diseases may, directly or indirectly, lead to a variety of dermatoses. As is well known, the liver is the second barrier against the infiltration of foreign substances through the digestive tract, the intestinal wall being the first. The liver can convert intermediary protein products foreign to the body either by conjugation or by breaking them down into substances which are normal to the body.

Hepatic insufficiency can lead to intestinal autointoxication in two ways: (1) as a result of the inability of the liver to detoxify an overwhelming amount of intestinal toxins or (2) as a result of liver damage which makes it impossible for that organ to cope with a normal volume of intestinal toxins, thus permitting the latter to enter the circulation and cause various disease processes. In addition to manifestations of hepatic decompensation arising in connection with the detoxification of poisons produced in the intestine, the liver may also fail, generally as a result of hepatic disease, to act as a filter for protein degradation products coming from the digestive tract, thus leading to manifestations of hypersensitiveness on the skin and other tissues. Dujardin and Decamps[567] as well as this writer, visualize the procedure as follows: Under normal conditions the liver is capable of intercepting nutritive allergens and of making them harmless, so that there can be no antigen-antibody reaction. However, in the event of hepatic insufficiency or of an overwhelming invasion of the liver by massive quantities of antigen, the liver is unable to deal with the situation (i.e., its proteopexic action is inadequate), whereupon antigen-antibody reactions in the form of allergic dermatoses or of other allergic manifestations may make their appearance.

It is readily comprehensible that a breakdown of one or more functions of the liver must have serious repercussions on certain organs of the body, including the skin, and even on the entire metabolism.

Discussed in some detail on page 291 are three distinct ways in which diseases of an internal organ and those of the skin can be interdependent. In accordance with this classification we shall now endeavor to present the interrelationship between the liver and the skin.

A. CUTANEOUS MANIFESTATIONS CAUSED BY HEPATIC DAMAGE DUE TO METABOLIC DISTURBANCES OR TOXIC METABOLITES

Icterus is unquestionably the best known and probably also the most striking cutaneous sign of liver damage. This condition is of importance not only because it so commonly constitutes the underlying cause of erythematous, urticarial, and pruriginous dermatoses, as well as of purpuric diseases, but also because the yellowish discoloration of the skin in itself represents a dermatosis, as do all other cutaneous pigmentary disturbances.

Icterus is associated with all types of hepatic disorders. The yellow pigmentation is brought about either (1) as a result of biliary obstruction, or (2) when more bile pigment is produced than can be eliminated by the liver, as in hemolytic jaundice, or (3) as a result of parenchymal disease of the liver. Eppinger feels that the latter group properly includes catarrhal jaundice, a condition which is no longer attributed solely to inflammation of the mucous membranes of the bile ducts, in the vast majority of cases, but which includes damage to the liver parenchyma. The various types of jaundice are not always distinct but may overlap in the same patient.

In addition to icterus, there are a number of other cutaneous discolorations, known as melanoderma, which accompany a variety of hepatic disturbances. Hemochromatosis, more commonly known as "bronze diabetes," refers to a dark pigmentation of the skin, which is seen in hypertrophic cirrhosis of the liver, accompanied by diabetes mellitus. The brown discoloration is caused by a pigment produced in the blood and is not due to bile. It is not to be confused with the entity "melanodermie biliaire" described by Gilbert and Lerebouillet,[790] seen in individuals with a family history of hereditary cholemia and of hepatic disease on

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790. GILBERT, A. and LEREBOUILLET, P.: Ann. de Dermat. 3: 915, 1902.

the order of hypertrophic cirrhosis. Furthermore, there is another type of pigmentation due to an underlying hepatic disorder consisting of discoloration, generally slate gray, of the buccal mucosa alone, without involvement of the skin (Sezary, Courbe, and Horovitz[791]).

Far more commonly encountered, however, are the localized pigmentations of the skin, particularly of the face, and called "liver spots" by the layman. Needless to say, not all of these must necessarily be regarded as an expression of some hepatic disturbance. However, such pigmentation, notably when occurring on the exposed parts of the body, makes it advisable to perform liver function studies. The clinicians of the old school called certain pigmentations "chloasma hepaticum" because the physical examination or autopsy findings convinced them that there was some connection between such cutaneous manifestations and the liver (Fig. 110). Individuals suffering from hepatic disorders not uncommonly present periocular pigmentation. These changes, termed "masque biliaire" by the French, present striking variations in intensity, ranging from light to

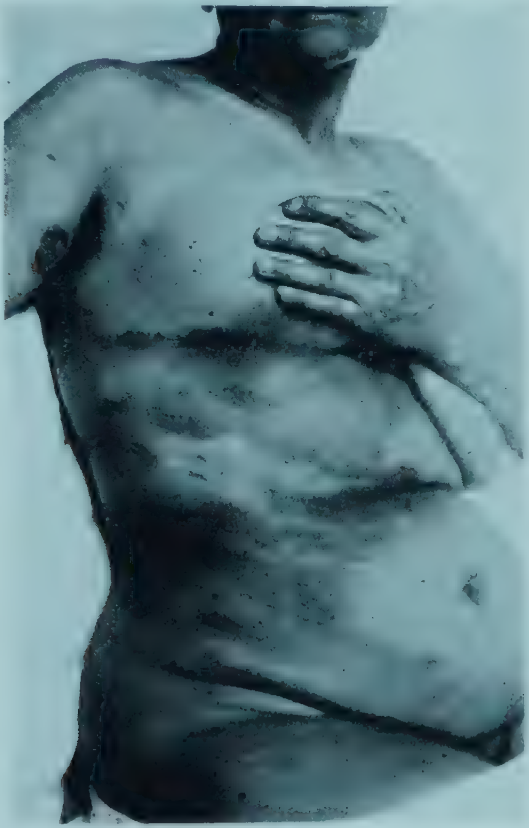

FIG. 110. HYPERPIGMENTATION DUE TO CIRRHOSIS OF THE LIVER

dark brown, and are most frequently seen in women with brunette complexion.

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[791] SEZARY, A., COMBE, and HOROWITZ, A.: Bull. Soc. franc. de dermat. et syph. 38: 774, 1931.

As for the chemical nature of the cutaneous discolorations other than icterus, the pigment consists of true melanin (in the stratum spinosum and in the pigment-bearing corium cells).

We shall now consider those skin diseases which occur as a direct result of icterus, the first being pruritus. It was formerly assumed that the itching of the skin in jaundice was attributable to the abnormal presence of bile salts in the blood, but this has not been established. In fact, it seems far more likely that the pruritus is due to metabolic by-products which are formed as a result of hepatic dysfunction and which make their way into the blood stream. Pruritus may begin long before the icterus and retrogress when the latter makes its appearance; in other cases, however, the itching does not set in until the jaundice has become quite pronounced, and may persist long after the icterus has faded; and in still other cases the two symptoms disappear simultaneously, especially following correction of biliary obstruction. On the other hand, one encounters cases of very pronounced jaundice in which there is no itching, while patients with only moderate jaundice may be tortured by the most intense itching. In short, there is no parallel between the degree of bilirubin retention within the organism and the occurrence or severity of pruritus. Individual factors obviously play an important role. The itching is especially intense in cases in which the bile ducts are obstructed by neoplastic disease.

The scratching induced by pruritus produces excoriations which often become secondarily infected, an occurrence which commonly complicates icterus. In addition, urticarial eruptions and, in especially severe cases, petechiae can be produced. Virtually identical cutaneous pictures have been observed in occasional cases of acute yellow atrophy of the liver.

Disturbances of secretion of bile by the liver play an important role in the production of skin diseases by way of the gastrointestinal tract, since bile is essential to the proper digestion of fat. However, as potential causes of skin diseases, the metabolic processes within the liver itself merit special attention. They include those which are concerned with the intermediary metabolism of food and those which involve the detoxification of poisons.

We cannot yet speak with certainty concerning the connection between impaired liver function and the dermatoses. However, it seems to be fairly definite that some of the cutaneous eruptions, such as generalized seborrheic dermatitis or exfoliative erythroderma, encountered in the course of chemotherapy (neoarsphenamine, gold, or sulfonamides) may be interpreted as being the result of complex deficiencies conditioned by impaired liver function. As an example of such a deficiency we may cite the relative inability of a diseased liver to metabolize protein and to utilize vitamins properly. In presenting this view, Gross[792] stresses the familiar fact that patients in a poor state of nutrition are not favorable subjects for chemotherapy. For instance, the hepatic function may be seriously impaired when there is depletion in dietary protein. Protein exerts a protective influence on the liver similar to the better known effect of glucose (Elman[310]). The more recently developed liver function tests permit us to evaluate more accurately the hepatotoxic effect of a given chemotherapeutic agent or of some other influence tending to damage the liver. Particularly the various tolerance tests may prove to be valuable for this purpose in the near future. Experimental work, such as that of Wiedmann,[793] may perhaps permit us to determine whether liver damage accompanying arsphenamine dermatitis, for example, is to be interpreted as a symptom of intoxication or of hypersensitiveness. For instance, parallel examinations of the carbohydrate and protein metabolism of the liver have shown that the presence of simultaneous disturbances of both functions can be regarded as evidence of a toxic influence, while a disturbance of the protein metabolism alone strongly suggests an underlying hypersensitiveness.

A consideration of the various liver function tests is of importance in connection with a discussion of the relationship between dermatoses and diseases of the liver. Unfortunately, there is no single test which will give us an adequate picture of hepatic activity, because of the multitude of metabolic tasks performed by this organ. It is therefore necessary to carry out quite a number of investigations in order to evaluate the principal biochemical functions of the liver. These fall into two main categories; those which concern the excretory powers and those which are related to the metabolic activities of the liver. For both categories there are numerous methods of testing, concerning which considerable controversy exists. We shall limit ourselves to those procedures with which we have had personal experience. Of value for determining the excretory power of the liver are such tests as the bromsulfalein test, the quantitative determination of the serum bilirubin or the bilirubin tolerance test, and the quantitative urine urobilinogen test. In order to gauge the different aspects of protein metabolism one should determine the serum protein fractions and employ the hippuric acid conjugation test, amino acid (glycocoll or glycine) tolerance test,* and the cephalin-cholesterol floccula-

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792. Gross, P.: Arch. Dermat. & Syph. **47:** 862, 1943.
793. Wiedmann, A.: Arch. f. Dermat. u. Syph. **173:** 173, 1935.

* The glycocoll (glycine) tolerance test seems to be of particular value in cases with light hypersensitiveness and liver dysfunction. These cases show an impair-

tion test. The carbohydrate metabolism can be studied by means of the galactose tolerance test and the glucose tolerance test. No reliable procedure exists for determination of fat metabolism in the liver.

The clinical observations made by authorities of the old school plus the liver function tests of the younger investigators would seem to support the view that many cases of dermatitis, urticaria, pruritis, skin pigmentation, and purpura are due to some disorder of the liver. A majority of our patients with light dermatoses presented symptoms of hepatic dysfunction. However, such a causal relationship must not be taken for granted merely on the basis of a suggestive history or because one or more of the liver function tests gives positive results. The connection may not be regarded as definitely established unless the patient also presents clinical or laboratory evidence of liver damage, or unless the treatment of the hepatic disorder is followed by marked improvement or cure of the liver condition with simultaneous retrogression of the cutaneous manifestations.

The literature contains numerous reports (Schur,[794] Menagh,[795] Goss,[796] Daniel,[797] Shay, Gershon-Cohen, and Fels,[798] Hansen-Pruess,[799] Urbach and Shay[800]) indicating that cholecystitis may be the sole cause of certain skin diseases, particularly urticaria and dermatitis, as evidenced by the disappearance of the cutaneous manifestations following cholecystectomy. Smithies[774] has reported gratifying results obtained in cases of severe dermatitis and urticaria by means of nonsurgical biliary drainage and a diet low in fat and protein. The present writer has seen excellent results achieved in pruritus and lichen urticatus of hepatic origin by a high carbohydrate, low fat intake, fortified twice daily by additional sugar (two tablespoonfuls), followed immediately by 10 to 15 units of insulin.

The presence of hepatic dysfunction has been studied by a number of

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ment of the capacity of the liver to deaminize amino acids, as evidenced by the fact that the glycocoll tolerance test revealed a rise of more than 50 per cent above the fasting amino acid level of the blood one hour after administration of 25 grams of glycocoll, or by the failure of the blood amino acid level to return to normal within three to four hours. The writer's investigations of this question have shown that the normal fasting amino acid blood level is approximately 7 mg. per cent (no more than 8 mg. per cent), that there is a rise of some 50 per cent after administration of 25 grams of glycocoll, and that the curve returns to its initial level within four hours at the most.

[794] Schur, H.: Wien. klin. Wchnschr. **40:** 81, 1927.
[795] Menagh, F.: J. A. M. A. **90:** 668, 1928.
[796] Goss, A. C.: Northwest. Med. **31:** 377, 1932.
[797] Daniel, I.: Arch. de mal. de l'app. digestif **22:** 30, 1922.
[798] Shay, H., Gerson-Cohen, J., and Fels, S.: Am. J. Digest. Dis. **6:** 335, 1939.
[799] Hansen-Pruess, O. C.: J. Allergy **9:** 577, 1938.
[800] Urbach, E. and Shay, H.: Ann. Allergy **3:** 124, 1945.

authors (Rocchini,[801] Kordowich,[802] Guldberg and Hannisdal[803]) in various ways, notably in dermatitis of unknown or of endogenous origin. Marquardt's investigations[804] seem to indicate that metabolic disturbances of the liver make it much more difficult to achieve a cure in many cases of chronically recurrent dermatitis. The writer has himself observed an instance of generalized erythroderma which exhibited high-grade water retention (cutaneous histohydria) and oliguria, accompanied by a severe impairment of the deamination function of the liver. The amino acid tolerance test with glycocoll (glycine) showed an increase in the amino acid level in the blood to 210 per cent of the original level as compared with the normal rise of 50 per cent. This case yielded to treatment consisting of liver injections plus a diet as described in the preceding paragraph. As Paul and von Vegh[805] have pointed out, parenchymal liver damage is generally accompanied by a disturbance of the water balance.

E. Hoffmann was the first to stress the connection between arsphenamine dermatitis and liver damage, a finding which was subsequently confirmed by Sicher and Wiedmann,[806] Doellken,[807] Milbradt,[808] and others. To be sure, Wiedmann[793] has demonstrated that the hepatic disturbance is not always the cause of the drug exanthem, but that the former may, under certain conditions, be the consequence of the allergic skin disease.

Barber and Oriel[751] reported good results achieved with a liver-sparing, high carbohydrate diet plus sugar by mouth and intravenously in case of neurodermatitis.

The cutaneous manifestations associated with cirrhosis of the liver merit special attention. Urbach[135] demonstrated that the itching which occasionally accompanies such skin symptoms is due to a disturbance of protein metabolism, as revealed by his chemical studies in which the skin showed an appreciable rise in nonprotein nitrogen, and the amino acid (glycine) tolerance test disclosed an abnormally high amino acid level in the blood. In accordance with these clinical findings, it has been noted that the subjective symptoms promptly disappear on a diet that is relatively low in protein, very low in fat, and high in carbohydrates. In addition, the diet should be high in calories and include an abundance of vitamins A, B, C, D, and K, but especially of the B complex. Exceptionally good therapeutic results were obtained when such a diet was

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801. Rocchini, G.: Giorn. ital. di dermat e sif. **76:** 1075, 1935.
802. Kordowich, F.: Arch. f. Dermat. u. Syph. **175:** 117, 1937.
803. Guldberg, G. and Hannisdal, L.: Arch. f. Dermat. u. Syph. **173:** 592, 1936.
804. Marquardt: Zentralbl. f. Haut- u. Geschlechtskr. **53:** 525, 1936.
805. Paul, B. and von Vegh, P.: Klin. Wchnschr. **15:** 1471, 1936.
806. Sicher, G. and Wiedmann, A.: Wien. klin. Wchnschr. **46:** 1049, 1933.
807. Doellken, H.: Arch. f. Dermat. u. Syph. **170:** 456, 1934.
808. Milbradt, W.: Med. Welt **9:** 1417, 1935.

supplemented with 50 Gm. daily of dried brewer's yeast (Patek,[809] Barker[810]). Moreover, cirrhosis of the liver is likely to be benefited by choline (6 Gm. daily) and inositol, or by foodstuffs rich in these factors (e.g., lecithin) (Woolley[811]).

A significant role is played by the liver in the intermediary disturbances which lead to the formation of porphyrins which, in turn, tend to allergize the skin to sunlight. In hydroa vacciniforme, for example, the cause of porphyrinopathy of hepatic origin is often to be found in a combination of lues and alcoholism. Thus, in a series of twelve cases of this disease, the present writer[812] found eight instances of alcoholism and syphilis combined, one or the other condition in three cases, and only one case in which there was neither lues nor alcoholism. In one instance we were able to prove that hydroa vacciniforme was due to photosensitization caused by luetic liver disease, by showing that appropriate antiluetic treatment simultaneously restored the previously abnormal galactose tolerance to normal levels, caused a cessation of porphyrin excretion in the urine, and made it possible for the patient to expose himself to sunlight with impunity. Needless to say, a course of antisyphilitic treatment will not always improve a case of a luetic cirrhosis of the liver to such an extent that the porphyrinopathy disappears. Newman[813] described the case of a man, aged 54, who suffered an attack of jaundice, with vomiting and upper abdominal pain. Two months later vesicles made their appearance on skin areas exposed to sunlight; the urine was found to contain an abundance of porphyrin.

Another clinical peculiarity presented by porphyrinopathies associated with cirrhosis of the liver is to be found in the fact that some of these patients develop a vesicular reaction, not only to exposure to sunlight, but also following mild trauma. This extreme vulnerability of the epidermis, which has been described by Gottron[813a] and Ellinger,[814] has also been observed by Schreus,[815] Cerutti,[816] and the writer. It is sometimes so pronounced that the slightest friction, such as commonly occurs while making up a bed, for example, will suffice to provoke the formation of vesicles or of denuding the epithelium with marked exudation. Gottron goes even further when he frankly attributes epidermolysis bullosa-like skin disease to luetic hepatopathy plus porphyrinopathy, while denying that sunlight has any connection with the cutaneous condition.

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809. Patek, A. J.: Bull. New York Acad. Med. **19:** 498, 1943.
810. Barker, H.: Med. Clin. North Amer. **29:** 273, 1945.
811. Woolley, D. W.: J. Biol. Chem. **147:** 581, 1943.
812. Urbach, E. and Bloech, J.: Wien. klin. Wchnschr. **47:** 527, 1934.
813. Newman, C.: Proc. Roy. Soc. Med. **29:** 47, 1935.
813a. Gottron, H.: Dermat. Wchnschr. **101:** 1305, 1935.
814. Gottron, H. and Ellinger, F.: Arch. f. Dermat. u. Syph. **164:** 11, 1931.
815. Schreus, H. T.: Klin. Wchnschr. **13:** 121, 1934.
816. Cerutti, P.: Arch. ital. di dermat. e sif. **11:** 3, 1935.

In a series of painstaking animal experiments, Suner and Perutz[817] were able to demonstrate that dogs with liver damage induced by phosphorus eliminate parenterally administered porphyrin in the urine, while similarly given porphyrin does not appear in the urine of animals with normal livers. Perutz[817] complemented these animal experiments with *in vitro* studies and showed, in confirmation of Suner's findings, that the healthy rabbit liver transforms the administered porphyrin into bile pigment, while the livers of animals poisoned by sulfonal are incapable of converting the porphyrin. Schreus and Carrié[818, 819] demonstrated the beneficial influence of raw liver, or of liver injections, in reducing the photosensitivity of animals receiving porphyrin. These authors observed that when rabbits, which had been eliminating increased amounts of porphyrin following sulfonal, were put on a diet of minced raw liver, the abnormal porphyrin excretion ceased and the cutaneous hypersensitiveness to ultraviolet light disappeared. Both Sellei and the present writer have observed gratifying results following parenteral liver therapy in a number of cases of hydroa vacciniforme due to liver damage.

The cutaneous hypersensitiveness which results from sensitization to porphyrin as a consequence of liver damage need not necessarily manifest itself in the form of hydroa but may very well take the form of dermatitis, urticaria, prurigo aestivalis, or erythema multiforme (see p. 514). Moreover, these cases do not invariably show porphyrin in the urine. On the contrary, the present writer has demonstrated that, not infrequently, porphyrinopathy can be established only by finding abnormal amounts in the stool. He described a group of cases of severe light dermatoses, presenting pictures of weeping and intensely pruritic dermatitis, of persistent erythemas, or of pellagra-like, diffuse pigmentations which, although demonstrably due to hypersensitiveness to light, failed to show any porphyrin in the urine, but revealed an abundance of porphyrin in the stool. Such fecal porphyrin is often the result of marked intestinal dysbacteria combined with a hepatopathy. Proof that the fecal porphyria is of alimentary (nutritional) origin, and not a manifestation of ulcerative intestinal lesions, is supplied by the fact that withdrawal of animal protein from the diet causes the cessation of porphyrin formation in the stool within a few days. Renewed administration of animal protein brings about a resumption of porphyrin production within forty-eight hours.

The presence of porphyrin in the stool can rapidly be determined with the aid of the fluorescent microscope, but the spectroscopic method must be used to verify the diagnosis. The finding of porphyrin in the stool may

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817. Perutz, A.: Arch. f. Dermat. u. Syph. **124:** 531, 1917.
818. Schreus, H.: Delib. 8th Internat. Dermat. Congress, 1930
819. Schreus, H. and Carrié, C.: Strahlentherapie **40:** 340, 1931.

be properly regarded as pathologic only when inspection with a fluorescent microscope reveals the presence of definite porphyrin crystals or of large, flaky, or irregularly shaped deep red deposits, or when the stool seems to be completely impregnated with red pigment. Moreover, hydrochloric acid and ether extracts of the stool must always be subjected to spectroscopic analysis, since porphyrin is not the only cause of reddish fluorescence. As the writer has shown,[788] the syndrome consisting of light dermatosis, fecal porphyrin, intestinal dysbacteria, and hepatopathy is not rare.

Porphyrin in human feces can be of exogenous or of endogenous origin. The exogenous porphyrin comes from two sources. In the first place, preformed porphyrin may be ingested with food of animal origin, especially when it contains blood, as occurs in meat, fowl, fish, or sausage. However, not only animal protein, but also vegetable products, especially grain and vegetables, contain porphyrin, although in small quantity. In the second place, spore-forming anaerobic bacteria in the intestine are particularly capable of producing porphyrin from the hemoglobin and myoglobin of ingested animal meat, as well as from the chlorophyll of vegetable foods, the latter yielding principally protoporphyrin. The quantity of porphyrin derived from bacterial action from the pigments in the food unquestionably constitutes the most important factor in the formation of porphyrin in the intestine. Lastly, porphyrin may be created endogenously from the so-called pyrroles by the synergistic action of certain intestinal bacteria in the intestine, even on a diet free of animal protein and chlorophyll.

According to Brugsch,[820] the stool normally contains 0.115 to 0.40 mg. of porphyrin, including principally coproporphyrin, protoporphyrin, and deuteroporphyrin as well as a porphyrin derived from the chlorophyll, the stercophorbid. Prophyrins are produced in the small intestine and in the upper segments of the large intestine. Both the ingested and the enterogenous porphyrins are to a very great extent absorbed through the walls of the intestine and carried by the portal system to the liver. This organ metabolizes and excretes them in the bile, partly as bilirubin and partly as coproporphyrin. The porphyrin not absorbed from the food and from the bile is eliminated in the stool.

Excessive exogenous porphyrin production is most commonly observed in association with abnormal anaerobic intestinal flora. Thus, severe cases of enteritis, colitis, and gastritis with anacidity not infrequently show increased porphyrin production in the intestine, without necessarily manifesting a corresponding rise in porphyrin in the urine. The increased formation of porphyrin in these patients can probably be explained by the fact that the lack of free hydrochloric acid and of important digestive ferments, together with the accompanying disturbance in the chemistry of the duodenum, favors putrefactive processes and thus leads to a change in the intestinal flora.

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[820] Brugsch, J. T.: Ztschr. f. d. ges. exp. Med. **95:** 471 and 482, 1935; **98:** 49 and 57, 1936.

Thus we see that although the porphyrin level of the stool shows an appreciable rise in a considerable group of gastrointestinal diseases, instances of hypersensitiveness to light, on the other hand, are relatively uncommon. In other words, pathologically increased fecal porphyrin does not necessarily lead to light hypersensitiveness.

Finally, we shall briefly consider the interrelationship of dysbacteria, liver diseases, and photosensitization. Hepatopathy alone rarely constitutes the sole cause of hypersensitiveness to light, as in the case of syphilis of the liver (Urbach and Bloech[812]). Thus, in most instances of photosensitiveness, liver therapy by itself is of limited value. The reason for this seems to be that in the presence of functional disorder of the liver that organ is unable to cope adequately with increased amounts of porphyrins produced in the intestine possibly as a result of dysbacteria, whereupon the porphyrins reach levels at which they cause hypersensitiveness to light.

The pathologic intestinal flora, comprising atypical and sometimes even hemolytic Bacilli coli, streptococci, an abundance of enterococci, and yeasts, found in cases with abnormally increased fecal porphyrin can often be normalized by a rather lengthy course of treatment with Bacillus acidophilus whey culture or with Mutaflor by mouth (Mutaflor consists of viable and very vigorous strains of B. coli). As the intestinal flora returns to normal, both the porphyrin formation in the stool and the hypersensitiveness to light disappear, provided the liver function improves. In practice, we were able to combat photosensitization by a procedure which, in addition to correction of the dysbacteria, includes treatment of the liver disease, notably by means of a low protein, low fat, high carbohydrate diet in combination with injections of crude liver and oral administration of brewer's yeast.

It may seem inconsistent to advocate a low protein regimen while the current practice in the treatment of liver diseases is to give a diet at least adequate, if not abundant, in protein. This is because our experience has shown repeatedly that a diet free of animal protein causes a disappearance of porphyrins and at the same time brings a great improvement of the clinical manifestations. The resumption of intake of foods of animal origin is followed in a day or so by reappearance of porphyrin and cutaneous symptoms.

Another group of dermatoses in which there is not infrequently a close

TABLE 75.—*Low Fat, Low Protein (Liver-sparing) Diet*

Purpose of the diet: (1) To protect the liver from toxic cleavage products produced in the bowel by bacterial action on dietary protein; (2) to reduce the demands on hepatic function necessary in the metabolism of fats and proteins; (3) to permit the liver to excrete substances which, when retained in the body, may produce manifestations in other tissues, such as cutaneous light hypersensitiveness.

The following foods are prohibited:

Fat meats, brains, kidneys, liver, sweetbreads; pickled or smoked meats
Fat, pickled, or smoked fish; fish roe
Fat poultry
Eggs
Cream
Fats, oils, shortenings, and foods containing them; salad dressing
All rich and highly seasoned foods
Salt and pepper at the table
Nuts, figs, dates
Whole wheat and bran products
Chocolate
Alcohol

The following foods are permitted:

Lean meat, fish, or poultry
Cottage cheese
All vegetables
All fruits
Bread, macaroni, spaghetti
Cereals
Jellies, jams, marmalade, preserves
Coffee, coffee substitute, tea, skimmed milk

(Not over 70 Gm. protein allowed daily.)

TABLE 76.—*Sample Menu for Low Fat, Low Protein (Liver-sparing) Diet*

Breakfast: Baked apple
Corn flakes with fruit and milk
Toast with marmalade
Coffee with milk and sugar

Luncheon: Consommé with barley
Macaroni with cheese, boiled squash, salad of lettuce and tomato with lemon juice and sugar
Canned, fresh, or stewed plums
Milk or tea

Dinner: Tomato juice
Small slice of lean roast beef
Baked potato, spinach, sliced beets
Mixed fruit cup
Coffee with milk and sugar

(Not over 70 Gm. protein allowed daily.)

connection with some hepatic dysfunction consists of those due to disturbances of the lipoid metabolism. These skin diseases include notably xanthelasma and xanthelasmatosis. (We[821] prefer these terms to xanthoma and xanthomatosis because cases of this kind very rarely present the blastomatous picture indicated by the suffix "oma.") The frequent simultaneous occurrence of xanthelasma and icterus induced the earliest observers to assume that there was some connection between these conditions. The work done in the past few years, however, has considerably enhanced our understanding of the relationship between hepatic dysfunction and xanthelasmatosis. Special mention must be made here of the valuable contributions of Bloch[822] and particularly of Schaaf.[823] According to the latter's experimental and chemical investigations, xanthelasmatoses are fundamentally attributable to faulty regulation of cholesterol and phosphatide metabolism. Interestingly, it is not the absolute quantity of lipoids but the abnormal ratios of the various constituents of the lipoid complex that play the important role here. Disturbances of the regulatory function, which is now believed to reside in the liver, can lead to a rise or fall in the cholesterol and phosphatide levels in the blood and can also change the ratio between free and ester cholesterol.

As Schaaf[823] has shown in his animal experiments, hepatic injury by irradiation or poisoning, together with a high fat diet, serves to bring on xanthelasmatosis. On the other hand, this Swiss author demonstrated experimentally that administration of a high fat diet alone, continued for some time, leads to liver damage and subsequently to the development of xanthelasma. This conforms with Huebner's report[824] of a patient who, after taking 1 to 1.5 liters of olive oil per month for one year, developed xanthelasmatosis.

In agreement with Schaaf, Nekam, Jr., and Ottenstein[825] regard hepatic dysfunction as the principal etiologic factor in the production of xanthelasma and attribute the damage to faulty deposition of cholesterol as well as to disturbance of cholesterol excretion, resulting in a change in the ratios of the lipoid fractions in the blood. These authors recommend the use of a low fat, high carbohydrate diet plus insulin for xanthelasmatosis, a regimen introduced by the present writer.[826]

Lastly, Wiedmann[827] has contributed an interesting new viewpoint per-

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821. Urbach, E. and Hill, W. R.: Arch. Dermat. & Syph. **42:** 68, 1940.
822. Bloch, B.: Brit. J. Dermat. **43:** 61, 1931.
823. Schaaf, F.: Arch. f. Dermat. u. Syph. **175:** 279, 1937.
824. Huebner, K.: Arch. f. Dermat. u. Syph. **171:** 571, 1935.
825. Nékam, L. Jr. and Ottenstein, B.: Klin. Wchnschr. **14:** 641, 1935.
826. Urbach, E.: Lipoidstoffwechselerkrankungen der Haut; in Handb. d. Haut- u. Geschlechtskr. ed. by J. Jadassohn. Berlin: Springer, 1932.
827. Wiedmann, A.: Arch. f. Dermat. u. Syph. **174:** 71, 1937.

taining to this problem. In a case of xanthelasma tuberosum he observed that the vitamin A level in the serum had risen considerably, and that it returned to normal following retrogression of the tumors. In this connection, Wiedmann points out that one of the liver's functions is that of converting carotene into vitamin A by producing carotenase with the aid of thyroxin. Under normal conditions the vitamin produced in this manner is stored in the liver and gradually given off; however, the diseased liver, according to this concept, is no longer capable of storing the vitamin A being produced.

TABLE 77.—*Low Cholesterol Diet*

Purpose of the Diet: To reduce the intake of cholesterol in the food to the lowest possible level, thereby preventing deposition of cholesterol in the tissues, particularly in the skin, as a result of disordered cholesterol metabolism.

The following foods are prohibited:

Fat meats, brains, kidney, liver, sweetbreads
Fat fish, fish roe
Fat poultry
Animal fats, including suet and lard
Eggs (yolk)
Butter
Oysters

The following foods are permitted:

Lean meats, fish, or poultry
Milk
Cottage cheese
Vegetables
Fruits
Jams, jellies, marmalade
Bread, noodles, macaroni
Cereals
Sugar, syrups, honey

In addition to the characteristic picture of xanthelasma or xanthelasmatosis there are a number of other cutaneous manifestations of disturbance of the lipoid metabolism, which are sometimes associated with hepatic disorders. Thus, Edelmann[828] has described a dermatosis characterized by yellow discoloration of the skin, without involvement of the scleras, and enlargement and tenderness of the liver. This condition is further marked by a spectacular degree of hypercholesterolemia. Adherence to a diet low in cholesterol serves to dispel the yellow pigmentation of the skin and reduce the blood cholesterol level to normal; resumption of a high cholesterol diet leads to a recurrence of the symptoms mentioned above.

Severe liver disease was also encountered in Buerger and Gruetz's[829] singular case of phosphatide cellular lipoidosis (see p. 548).

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[828] EDELMANN, A.: Wien. med. Wchnschr. **78:** 1350, 1928.

[829] BUERGER, M. and GRUETZ, O.: Arch. f. Dermat. u. Syph. **166:** 542, 1932.

In a patient with extracellular cholesterosis described by the present writer,[110] the liver was not found to be enlarged although the liver function tests unmistakably pointed to the presence of hepatic disease. In some of these disturbances of the lipoid metabolism, gratifying results have been obtained with a liver-sparing regimen consisting of a low cholesterol, high carbohydrate, moderate protein diet augmented by insulin therapy.

B. LIVER DAMAGE CAUSED BY SKIN DISEASES

In order to determine whether skin diseases are due to hepatic dysfunction or vice versa, Matsunobu[830] performed a series of liver function tests on patients with dermatitis and on rabbits with experimentally induced dermatitis. He concluded that although 30 per cent of the dermatitis cases presented some hepatic dysfunction, the liver disturbance was the cause in only a part of them, while in the others it was evidently the result of the skin diseases. Matsunobu drew these conclusions from the outcome of his animal experiments, in which he found that the liver function often deteriorated following the appearance of experimentally induced dermatitis, only to improve when the cutaneous manifestations had retrogressed. Tanae[831] examined the livers of rabbits with dermatitic skin lesions produced by application of croton oil, and discovered that the liver tissue had been affected by the inflammatory process in the skin. All degrees of hepatocellular damage were encountered, even including total absence of glycogen as well as deposition of neutral fat in the liver lobules. It is noteworthy that the hepatic symptoms were most pronounced during the

TABLE 78.—*Sample Menu for Low Cholesterol Diet*

Breakfast:	Stewed prunes Farina with milk and sugar Rolls with jelly or marmalade Coffee with milk and sugar
Luncheon:	Asparagus, mashed potato, cottage cheese Salad with vinegar or lemon juice and sugar Bread with jelly Stewed pears Milk or tea
Dinner:	Lean meat or fish Boiled rice moistened with bouillon; green beans, broccoli Rolls or bread Gelatin dessert with fruit ice Coffee with milk and sugar

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[830] MATSUNOBU, T.: Jap. J. Dermat. & Urol. **30:** 86, 1930.
[831] TANAE, N.: Jap. J. Dermat. & Urol. **38:** 100, 1935.

subacute stages of the cutaneous inflammations. Milbradt[832] has also observed liver damage due to resorption of toxic products resulting from severe, artificially produced skin inflammations. Moreover, it is known that, in man, minute necrotic lesions develop in the liver following extensive skin burns. Luniatschek[833] made use of the glycogen and glutathione content of the liver as indices of chemically demonstrable hepatic changes associated with superficial, experimental croton oil dermatitis. It is well established that the glycogen content of the liver is a measure of its efficiency, while glutathione possesses the capacity to detoxify poisonous substances. Luniatschek found that at the peak of the cutaneous inflammation, which occurred on the fifth day, the glycogen level in the liver showed a 50 per cent drop, while the glutathione level had risen appreciably; the chemical changes showed a definite parallelism with the duration and intensity of the dermatitis. These liver findings may be interpreted either as a reaction to the resorption of toxic proteolytic products arising in the inflamed skin, or as a reaction of the metabolism to irritation of the vegetative nervous system by the dermatitis. The first assumption would seem to be supported by the fact that injections of extracts from the inflamed skin are capable of exerting a harmful influence on the livers of experimental animals (Miyake and Takada[834]).

The facts presented above are readily understandable in view of Urbach and Sicher's[12] extensive experimental investigations which demonstrated that many different chemical and physical inflammatory processes in the skin lead to proteolytic changes in the cutaneous tissue. This also serves to explain why so many acute skin diseases, including notably exfoliative dermatitis, arsphenamine dermatitis, generalized dermatitis, chronic urticaria, and some forms of psoriasis are associated with hepatic dysfunction which disappears as the cutaneous manifestations retrogress (Doellken,[807] Ijichi[835]).

Lastly, Stroebe's findings[836] are particularly interesting. This investigator discovered that cutaneous manifestations of an anaphylactic character are capable of producing functional disorders of the liver, just as more or less severe liver damage can be demonstrated in experimental anaphylactic shock in animals and in analogous conditions in man.

C. HEPATIC AND CUTANEOUS DISTURBANCES AS CONCOMITANT SYMPTOMS OF A COMMON UNDERLYING DISEASE

In a number of diseases with cutaneous symptoms plus signs of hepatic disorder, these manifestations are both due to the same underlying toxic

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832. Milbradt, W.: Dermat. Wchnschr. **101:** 595, 1935.
833. Luniatschek, V.: Arch. f. Dermat. u. Syph. **175:** 78, 1937.
834. Miyake, I. and Takada, I.: Jap. J. Dermat. & Urol. **33:** 421, 1933.
835. Ijichi, K.: Jap. J. Dermat. & Urol. **35:** 611, 1934.
836. Stroebe, F.: Ztschr. f. klin. Med. **120:** 95, 1932.

or infectious etiology. This is particularly true of cases in which the onset of the skin and hepatic processes is acute. Thus, there is no doubt that in dermatitis and hepatocellular disease incident to the administration of arsphenamine, gold, sulfonamides, and other potentially toxic agents, both are concomitant results and are not related as cause and effect. The same relationship seems to exist in hemochromatosis, which is a chronic disease characterized by a triad of symptoms consisting of a bronze-like color of the skin, cirrhosis of the liver, and glycosuria. Authorities in the field of pathologic anatomy are now of the opinion that the hepatic condition and the bronze pigmentation of the skin are due to the same metabolic causes. The peculiar discoloration of the skin and scleras, which is brownish yellow to begin with and later assumes a faintly bluish green tinge, is due not to bile pigment alone, but also to the iron-bearing pigment hemosiderin. The urine often contains an abundance of hematoporphyrin.

Another example of concomitance of skin and liver lesions may be presented by the multiple angiomas which appear in the final stages of cirrhosis of the liver (van Bogaert and Scherer[837]). Moreover, these authors as well as Milbradt, Weil, Lortat and Boutelier, and the writer found hereditary hemorrhagic telangiectasis of Osler associated with cirrhosis of the liver. It is reasonable to assume that the cutaneous as well as the other lesions of this hereditary disease are not caused by the liver disorder which occurs late in life, but that both are dependent upon a common etiology.

D. LIVER THERAPY IN SKIN DISEASES

The gratifying results obtained with liver therapy in a wide variety of pathologic processes and the great importance of the liver as a detoxifying organ suggested the use of this therapeutic approach in skin diseases, particularly in those which may be regarded as a consequence of hepatic dysfunction. Spiethoff[838] was the first to report favorable results with this method in arsphenamine dermatitis in man. Moreover, he and his co-worker, Milbradt, were able to demonstrate in animal experiments that administration of liver definitely exerts a curative influence if hepatocellular damage has been caused by arsphenamine, bismuth, or mercury. Indeed, the beneficial effect of liver administration is so great that in cases of incipient dermatitis this form of therapy makes it possible to continue the antisyphilitic treatment with impunity, in so far as the skin is concerned (MacKee and Astrachan[839]). The beneficial therapeutic effect of liver extracts in arsphenamine dermatitis was confirmed by Wiedmann.[793] In his interesting experimental work this investigator examined animals which were sacrificed after having received large doses of liver extract parenterally in combination with subtoxic doses of arsphenamine. It was found that amounts of this arsenical (4 to 8 Gm.) which, in unprotected animals, regularly led to fatal poisonings and total depletion of the liver glycogen, failed to have such toxic effects in those which have received liver. In fact, their hepatic glycogen was even higher than normal. It would seem, therefore, that the administration of liver extract induces glycogen fixation, which protects the liver. The process by which this is accomplished has not as yet been explained.

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[837] van Bogaert, L. and Scherer, J.: Ann. de Med. **38:** 290, 1935.

[838] Spiethoff, B.: München. med. Wchnschr. **76:** 577, 1929.

[839] MacKee, G. M. and Astrachan, G. D.: J. Invest. Dermat. **3:** 409, 1940.

According to Spiethoff,[838] liver therapy in psoriasis serves to reduce the reactivity to external and internal excitants; this beneficial action ceases, however, when the quantities of liver are inadequate or when administration of liver is suspended. Spiethoff attributes the favorable results in these cases to substitution therapy, i.e., supplying lacking liver factors to the organism. Spiethoff believes, furthermore, that this treatment is also beneficial in some forms of pruritus and other skin diseases. Gross[840] advocates the administration of crude liver extract in addition to yeast and wheat germ in erythemato-squamous dermatoses, including psoriasis, seborrheic dermatitis, and pellagroid eruptions.

Sutton[841] recommends liver therapy in cases presenting deep-seated acne nodules, as well as in chronic furunculosis. Good results obtained with parenteral liver injections in hydroa vacciniforme have been reported by Schreus as well as by Urbach and Bloech.[812]

Lastly, Sydenstricker and associates,[842] Rudy and Hoffman,[224] and Gross[225] are of the opinion that in the treatment of cutaneous diseases incident to diabetes a combination of parenteral liver extract and appropriate vitamin therapy is preferable to diet plus insulin.

E. DERMATOSES CAUSED BY DISEASES OF THE PANCREAS

The significance of pancreatic dysfunction in the production of dermatoses has been pointed out by Ehrmann, Ayres,[843] Cheinisse,[844] Rueda,[845] and other workers.

Since the pancreas constitutes the keystone of the entire alimentary apparatus, and the digestion of all three groups of foodstuffs, proteins, fats, and carbohydrates, is accomplished mainly by ferments secreted by that organ, pancreatic dysfunction soon leads to serious disorders. Impairment of fat digestion occurs first, and digestion of the protein is also incomplete. The latter leads to abnormal putrefactive processes and per-

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840. Gross, P.: Clinics **3:** 789, 1944.
841. Sutton, R. L.: Arch. Dermat. & Syph. **18:** 887, 1928.
842. Sydenstricker, V. P., Geeslin, L. E., and Weaver, J. W.: J. A. M. A. **113:** 2137, 1939.
843. Ayres, S. Jr.: discussion to Stokes and Pillsbury[734].
844. Cheinisse, L.: Presse med. **31:** 811, 1923.
845. Rueda, P.: Semana med. **31:** 1190, 1924.

sistent enteritis which is refractory to treatment. Disturbances in pancreatic function may be primary, i.e., arising within that organ itself, or secondary to a cause outside the pancreas, such as inadequate gastric secretin formation. In the former it is necessary to give the patient pancreatin. In the latter, administration of hydrochloric acid and pepsin, taken while the food is being eaten, can readily correct the lack of these substances; but it is also necessary to give pancreatin, half an hour after the meal, as an adjuvant therapeutic measure.

Markel[846] has described a patient with recurrent urticaria and angioneurotic edema, whose stool was typically fatty and contained undigested meat fibers. Deficient production of steapsin and trypsin was the cause of the elimination of undigested fats in the feces and of the absorption of incompletely digested protein. When the patient received pancreatin in doses of 1 Gm. three times daily the cutaneous manifestations disappeared. They recurred, however, when pancreatin was stopped.

While this case was one involving a primary disturbance of the pancreatic secretion, in an instance described by Kauders[847] the pancreatic insufficiency was secondary. In this patient, who had suffered with generalized dermatitis for five years, Kauders found hypo-acidity and mushy stools containing connective tissue and a great deal of imperfectly digested muscle fiber. On a meat-free regimen and administration of hydrochloric acid the patient's skin disease cleared up. When meat was permitted without hydrochloric acid there was a recurrence of the dermatosis. From these facts Kauders concluded that the dermatitis was caused by hypochylia of the pancreas secondary to gastric hypo-acidity.

Occasional cases of food allergy with cutaneous manifestations can be controlled completely by administration of hydrochloric acid and pepsin plus pancreatin (Bradley and Belfer,[848] Urbach[26]). If the skin lesions disappear, pancreatin is omitted in order to determine the extent to which the pancreas is involved in causing the dermatoses.

The enzyme-producing organs are correlated with other glandular organs of external and internal secretion. Therefore, qualitative and quantitative disturbances of enzyme production can lead to disorders not only in the gland in question, but also in other and remote structures which may, in turn, bring on other diseases. Sellei[849] coined the term "dysfermentoses" to designate the group of diseases arising in other tissues as the result of abnormal enzyme secretion, such as the skin, bone marrow, and nervous system, and advocated ferment therapy for the treatment of these conditions.

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[846] Markel, J.: Arch. Dermat. & Syph. **39:** 992, 1939.

[847] Kauders, F.: Wien. med. Wchnschr. **71:** 1602, 1921.

[848] Bradley, H. C. and Belfer, S.: Am. J. Digest. Dis. **5:** 730, 1939.

[849] Sellei, J.: Brit. J. Dermat. **46:** 523, 1934.

According to Sellei, the dysfermentoses include notably scleroderma and diffuse idiopathic atrophy. In the former, he claims to have demonstrated the presence of a disturbance of pancreatic secretion, by determining the atoxyl-resistant lipase. Administration of fresh or dried pancreas, as well as of other digestive ferments, led to improvement since the indurated areas first softened and then disappeared. No improvement can be achieved, however, in cases where the disease has already progressed to the atrophic stage, or where myosclerosis has caused fixation between skin and muscle tissue. Moreover, it is of no value in acrosclerosis (Sellei's term for sclerodactylia), which, in his opinion, is not true scleroderma, but a vascular disease.

According to Sellei, ferment therapy is based on a "chemical system" composed of enzymes, ascorbic acid, and metallic catalysts. Such therapy is effective only when the enzymes and other preparations are fresh and administered in sufficient quantity and uninterruptedly for some time. Moreover, the ferments must never be taken on a full stomach, but preferably one and one-half hours before meals. Sellei's dosage is as follows: breakfast, 150 to 200 Gm. of raw pancreas (mixed with mayonnaise, or leafy green vegetables containing ascorbic acid or sweet peppers, tomatoes, cucumbers, or an anchovy spread, or mushrooms). The remaining meals are left to the choice of the patient. However, with every repast there must be taken three pancreatin tablets, ascorbic acid, and iron. After a few weeks the raw pancreas is replaced by pancreatin tablets and still later by raw liver (200 to 250 Gm. daily) prepared as just described for the pancreas.

Although Sellei's theory is certainly interesting, work has not been repeated sufficiently to permit a proper evaluation of this approach. However, Becker and Obermayer[269] reported satisfactory results in two cases of generalized superficial scleroderma with the administration of raw pancreas.

Skin diseases are far more commonly caused by inadequate internal secretion of the pancreas, i.e., by diabetes mellitus, than by a deficiency of its external secretion. The role of disturbances of carbohydrate metabolism in the production of dermatoses was discussed in Chapter II, page 71.

PART FOUR

NUTRITIONAL THERAPY OF SKIN DISEASES

In the following pages we shall endeavor to present an outline of nutritional therapy for skin diseases, established on the basis of experimental and clinical evidence. However, at the very beginning it must be stressed that there is no specific form of dietary for most dermatoses; in other words, there is no special diet for dermatitis, psoriasis, acne, or other cutaneous disorders.

The diet can exert its influence as an adjuvant factor in the treatment of skin diseases in six different ways, namely: (1) in correcting the fundamental cause in dermatoses due to avitaminoses, malnutrition, functional disturbances or diseases of the digestive organs, or metabolic anomalies; (2) in eliminating the underlying factor in cases of specific hypersensitiveness to foods; (3) in lending support to other measures designed to modify the chemical composition of the skin and thereby its biologic reactivity; (4) as an auxiliary therapeutic measure in those cases where the patient's physical or constitutional status calls for a suitable dietary which will, for example, promote a gain in weight in thin persons or a weight reduction in overnourished individuals; or (5) in still other cases, to achieve a nonspecific alteration of the organism (*Umstimmung*) by means of alternate administration of radically dissimilar forms of diet; and (6) to enhance resistance to infection by means of adequate nutrition and, particularly as Cannon[850] and Clausen[851] have shown, by an abundance of proteins of high biologic value and of food rich in vitamin.

In nutritional therapy, more perhaps than in any other form of treatment, particular attention must be paid to the pathogenesis of the condition under consideration, and especially to the patient's constitutional type and state of nourishment. The pathogenesis will determine to what degree dietotherapy enters into the case. When planned and carried out strictly in accordance with the individual requirements of the case, nutritional therapy may be an important part, sometimes even the essential factor, of the management of a dermatosis. However, it must be remembered that only in very recent times have dietary regimens been employed scientifically in the treatment of skin diseases, so that we are just beginning to appreciate the value of this approach. Nevertheless, a great number of pertinent observations have already been reported in a large variety of dermatoses. These reports will now be summarized and critically discussed.

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[850] Cannon, P. R.: J. A. M. A. **128:** 360, 1945.

[851] Clausen, S. W.: Physiol. Rev. **14:** 335, 1934.

It is not an easy matter to group the dermatoses for this particular purpose. We have endeavored to classify them, as far as possible, on the basis of their pathogenesis. Where this is not feasible, the dermatosis in question is discussed separately.

CHAPTER VIII

Dermatitis (Eczema)

THE relatively great amount of space which will be devoted to the discussion of the relationship between nutrition and dermatitis may serve as the best indication of the close connection between the diet and skin diseases of this type. Nutritional therapy is of prime importance in certain groups of dermatitides, while in others it is useful as an adjunct—for instance, for dehydration purposes. Even in the former, however, it would be an error to neglect other forms of treatment, notably topical measures.

The main difficulty encountered by the physician in prescribing nutritional therapy lies in the fact that the appropriate diet is bound to vary considerably from case to case in accordance with the nature of the underlying cause. This brings us to the very core of the entire problem, namely, the basis on which to classify the dermatitides into various groups or categories. Since our therapeutic approach is essentially etiologic, the classification should be made not along morphologic but, if possible, along pathogenetic lines.

Until recently the term "eczema" was generally used for acute and chronic inflammations of the skin distinguished by certain rather characteristic clinical and morphologic features produced, however, by a multitude of factors. It has been proposed in the past few years that the name "eczema" be restricted to those cases in which the cause was either internal or unknown, while the term "dermatitis" be applied to those with external or known etiology. Obviously, this differentiation is artificial. Thus, the cutaneous manifestations produced by sulfonamides taken internally would be called eczema while those resulting from external application of the same substance would be termed dermatitis. Moreover, the differentiation between eczema and dermatitis would depend on the diagnostic acumen of the physician. For these and other reasons it has often been suggested that the designation "eczema" be dispensed with entirely, and that it be replaced by the term "dermatitis" amplified by an adjective indicative of the known or presumed etiology. The present writer has strongly favored discontinuing the use of the word "eczema." However, despite all the progress made in the recognition of the pathogenesis of the dermatitides, we are still obliged to resort to morphologic criteria to some extent, necessitating the use of such expressions as "neurodermatitis," "infantile dermatitis," and the like.

Numerous attempts have been made to classify the dermatitides. Sulzberger,[852] Stokes,[440] Bonnevie,[853] Burckhardt,[854] and Robinson[855] have contributed the most significant studies in this direction.

We suggest that the dermatitides be divided into eight principal groups, as follows:

1. Contact Dermatitis (syn. epidermatitis,* epidermitis†)
    a. toxic contact dermatitis
    b. allergic contact dermatitis
2. Allergic Dermatitis (from within)
    a. due to food
    b. due to drugs
3. Dermatid‡ (autosensitization dermatitis)
4. Metabolic Dermatitis
5. Neurodermatitis
6. Infantile Dermatitis
7. Seborrheic Dermatitis
8. Infectious and Parasitic Dermatitis

From this classification it will be seen that all groups are based on pathogenetic grounds except neurodermatitis and infantile dermatitis, where we were obliged to resort to clinical criteria. This is necessary because these two groups are clinical entities in which the pathogenesis may vary from case to case.

The groups outlined above do not by any means represent sharply defined clinical pictures. On the contrary, transitional forms are frequently encountered, so that it is often difficult to know, for example, whether one is dealing with a case of infantile dermatitis or with one of seborrheic dermatitis in an infant. Moreover, one and the same patient may very well present two types of dermatitis simultaneously, e.g., contact dermatitis and neurodermatitis. Despite all these difficulties, every effort should be made to classify the presenting case correctly, for this is essential to therapy based on etiologic considerations.

For obvious reasons, we shall confine our discussion to those categories of dermatitis which are either directly or indirectly related to the diet.

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* The term "epidermatitis" was introduced by Templeton.[576]

† Epstein[856] suggested the shorter term "epidermitis."

‡ This term was coined by Jaffrey[857] for hypersensitiveness to skin products which have become foreign to the body.

852. Sulzberger, M. B.: Dermatologic Allergy. Springfield, Ill.: Thomas, 1940.
853. Bonnevie, P.: Aetiologie und Pathogenese der Ekzemkrankheiten. Copenhagen: Barth, 1939.
854. Burckhardt, W.: Dermatologica **81:** 196, 1940.
855. Robinson, H. M.: Clinics **3:** 834, 1944.
856. Epstein, S.: Ann. Allergy **2:** 247, 1944.
857. Jaffrey, W. R.: Canad. M. A. J. **37:** 478, 1937.

For purely didactic reasons, dermatitis in adults and that in infants and small children will be considered separately.

Before therapy based on etiology can be prescribed, the patient must of course be meticulously and painstakingly examined. The appropriate form of nutritional therapy in a given case will depend on the presence of functional or organic disease of the gastrointestinal tract, signs of metabolic disorders or of hypersensitiveness, or other conditions. Furthermore, in addition to causal nutritional therapy, the physician will naturally prescribe local measures as well, particularly in view of the fact that in many instances the underlying organic disturbances do not directly provoke the dermatitis but rather exert their influence on the entire organism, predisposing the latter to the dermatitis-producing action of external excitants.

A. CONTACT DERMATITIS (EPIDERMATITIS, EPIDERMITIS)

It is clearly evident that the responsible exogenous cause must be eliminated in every instance of contact dermatitis before any kind of improvement, not to say cure, can be expected. However, appropriate nutritional therapy can to some extent bring rapid and definite improvement in cases with extensive, acute manifestations.

Schwartz[857a] suggested the possibility that a worker's diet influences the susceptibility of the skin to external irritants. He believes that this may be achieved chemically by changes in the pH of the sweat. This in turn alters the solvent and neutralizing action of the sweat on external irritants. Thus if a workman is exposed to an alkaline contactant while his sweat is markedly acid, that irritant would tend to be neutralized. On the other hand perspiration of alkaline reaction would enhance the irritant action of such a contactant.

Many years ago, Bulkley[5] strongly recommended a complete fasting cure for acute dermatitis. Chevallier[858] observed that previously ineffective local measures soon brought satisfactory results when supported by fasting cures (two or three days of total abstinence from food). Dardel[190] and Meyer[70] were the first to prescribe a strict milk diet for a few days in the treatment of acute inflammatory conditions of the skin. This regimen has also brought excellent results in the hands of Perutz,[859] Chiale[192] and the present writer (Figs. 111, 112). We therefore regularly prescribe a strict milk and distilled water diet for two or three days in connection with the etiologic treatment of cases of extensive acute epidermatitis. This dietary is described in detail on page 62. When milk is not tolerated, similarly good results may be obtained with a regimen employing fruit juices (p. 64).

[857a] Schwartz, L.: Indiana State M. A. **31:** 379, 1938.

[858] Chevallier, P.: Bull. Soc. Franc. de Dermat. **33:** 487, 1926.

[859] Perutz, A.: Arch. f. Dermat. u. Syph. **163:** 295, 1931.

The efficacy of the Dardel-Meyer milk diet is largely attributable to the fact that it serves to reduce the water and chloride content of the skin. That so much water and sodium chloride can be lost is explained by our own findings, which demonstrate that in dermatitis patients the pathologic and the clinically normal skin areas alike contain relatively great quantities of water and table salt. Many years have passed since Brocq and S. Jessner called attention to the importance of a salt-poor diet in acute dermatitides. Doerffel[71] achieved equally good results with the salt-poor diets of Gerson and Sauerbruch-Herrmannsdorfer (p. 65). Ballestero and Mom[189] demonstrated that a low chloride diet has a favorable influence on the course of experimentally produced contact dermatitis. Zorn and Popchristoff[860] observed definite disturbances of chloride excretion in patients with dermatitis and noted that retention begins prior to the skin eruption. Therefore the author feels that there is good reason to prescribe a low salt diet in the eruptive stage of epidermatitis.

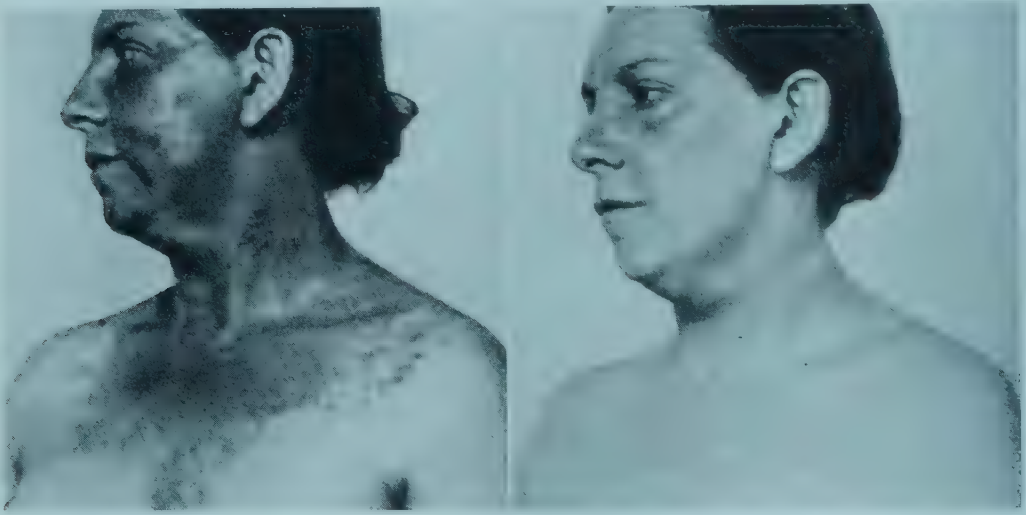

FIG. 111 FIG. 112

ACUTE DERMATITIS TREATED WITH MILK DIET

FIG. 111. Appearance before therapy.

FIG. 112. After three days of diet consisting exclusively of 1 liter of milk and 1 liter of distilled water. No local therapy.

In this connection, we must not fail to call attention to the gratifying results achieved with raw food diets by Schittenhelm, Bircher-Benner, and others. However, Veil, for one, warns against prolonged continuation of a one-sided vegetable diet. Mention must also be made here of the occasional good results which may be obtained with Schroth's hunger and thirst diet in the treatment of dermatitis (p. 124). Furthermore, alkalinizing treatment has often been given in connection with a salt-poor diet; and Dinkin,[861] Patkanjan,[862] and others claim to have achieved good results with this combination.

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[860] ZORN, R. and POPCHRISTOFF, P.: Ann. de dermat. et syph. 5: 637, 1934.

There is surely no need to stress the well known fact that alcohol, stimulants such as strong coffee and tea, and highly spiced and salty foods are absolutely contraindicated in cases of acute dermatitis.

When we consider the fact that in one instance total abstinence from food, in another a diet of raw foods, and in still another an alkalinizing diet leads to marked improvement, we must inevitably arrive at the conclusion that the common factor which promotes amelioration in acute epidermatitis lies in the rapid changes in the blood and tissue reactions brought about by any radical alteration in the diet. The abrupt metabolic shift makes for an *ictus therapeuticus* which cannot be achieved in any other manner. In other words, all of these diets seem to belong to the group of the alteration (*Umstimmung*) diets (see p. 124).

B. ALLERGIC DERMATITIS FROM WITHIN

This group comprises the dermatitides which are fundamentally due to hypersensitiveness to food or drugs.

1. Allergic Dermatitis Due to Food

It is becoming increasingly evident that dermatitides may be due to food allergy. The reason that this etiologic relationship is not properly appreciated is that the diagnostic procedure generally used is utterly unreliable. We refer, of course, to the skin tests, both the intracutaneous and the scratch methods, which are equally fallible whether their results are positive or negative. However, the elimination diet and the Propeptan diet offer dependable means of determining food allergies. They are discussed in some detail on pages 243 and 251. Before presenting illustrative cases which demonstrate the importance of food allergy in dermatitides, we desire to express our preference for the Propeptan method for their treatment. The etiologic, diagnostic, and therapeutic aspects of dermatitis due to food allergy are so closely linked that it is not feasible to consider them separately. The reader is therefore referred to the detailed presentation on pages 202–76.

There have been numerous reported cases of subacute and chronic dermatitides (other than neurodermatitis) due to foods. Thus, Hazen[604] observed the case of a 19 year old girl who had suffered uninterruptedly from chronic dermatitis since her first year of life, with the exception of

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861. Dinkin, L.: Deutsche med. Wchnschr. **54:** 228, 1928.
862. Patkanjan, K.: Russk. Vestnik. Dermat. **6:** 666, 1928.

one period during which she lived on a small island where milk was not available. Experimental investigation revealed that ingestion of minute traces of cream could elicit the skin manifestations, while the patient remained free as long as milk was strictly avoided. Ramirez[863] reported a case of dermatitis of the hand in a patient who ate bananas every morning; the skin involvement disappeared when the patient avoided this fruit, but promptly reappeared when he resumed eating it. Ratner[864] described dermatitides due to ingestion of egg protein and of milk; Grenet and Clement,[865] cases involving bread; Chargin,[866] flour; and Kipp,[867] rye bread. Similarly, Rowe,[25] employing his elimination diet method, repeatedly demonstrated both wheat and milk to be causes of dermatitis. Hopkins and Kesten[656] reported cases due to chicken and venison, respectively. Vallery-Radot and Heimann[868] achieved complete cure of a dermatitis, which had persisted since early childhood, by eliminating potatoes from the diet. Tyson observed dermatitides due to ingestion of oranges; Spitzer, cases due to strawberries. Lastly, mention should be made of observations reported by Adelsberger and Munter:[572] Fruit and grain dealers of both sexes, who had been allergized to fruit or flour by their occupational exposures, subsequently developed an alimentary allergy expressed by dermatitis (sometimes with asthma or angioneurotic edema). The present writer made similar observations among lemon sorters, and Schoenhof among asparagus workers.

Of the writer's own cases of dermatitis due to nutritive allergy, a few appear to be worthy of special mention. One is of particular interest because it afforded him, in collaboration with Fasal,[869] the opportunity of advancing the first recorded experimental proof that there is such an entity as nutritive allergic dermatitis, by fulfilling all of the criteria necessary for a scientific demonstration of an allergic etiology.

The patient, a 22 year old woman, had been suffering for eleven months from chronic dermatitic skin disease and intense pruritus on the back and sides of the neck (Figs. 113, 114), on the extensor aspects of both thighs, and in other areas. Since the history included mention of an aversion to eggs, this food was excluded from the diet, whereupon the skin improved. Then the patient was given two eggs. Within an hour she began to complain of unbearable itching, and simultaneously the dermatitic manifestations, which had almost disappeared, recurred at all the former sites. Strict elimination of eggs from the diet resulted in complete cessation of the pruritus and marked retrogression of the inflammatory lesions within forty-eight

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863. Ramirez, M.: Arch. Dermat. & Syph. **2:** 365, 1920.
864. Ratner, B.: M. Clin. North Amer. **6:** 815, 1922.
865. Grenet, H. and Clément, R.: Bull. et mém. Soc. méd. d. hôp. de Paris **47:** 814, 1923.
866. Chargin, L.: Arch. Dermat. & Syph. **6:** 222, 1922.
867. Kipp, R.: Med. Welt **8:** 1765, 1934.
868. Vallery-Radot, P. and Heimann, V.: Hypersensibilités specifiques dans les affections cutanées. Paris: Masson, 1930.
869. Urbach, E. and Fasal, P.: Arch. f. Dermat. u. Syph. **164:** 133, 1931.

hours. Oral administration of egg repeatedly and regularly elicited the appearance of the cutaneous symptoms, while intracutaneous injection, even of concentrated egg white, evoked no local reaction.

That this case was one of nutritive-allergic dermatitis was most conclusively demonstrated, however, by the fact that it was possible to transfer the patient's dermatitis to a recipient who had previously responded negatively to a test for hypersensitiveness to egg. Figure 115 shows the dermatitic reaction of the recipient twenty-six hours after it first appeared. At this time the cutaneous manifestations elicited by the test consisted of a sharply defined erythematous and elevated area

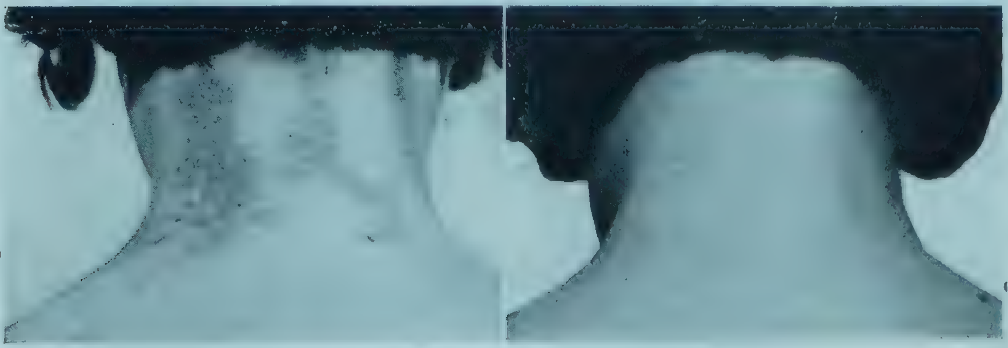

Fig. 113 Fig. 114

Chronic Dermatitis of the Neck on the Basis of Egg Allergy

Fig. 113. Appearance before treatment.

Fig. 114. Complete remission of cutaneous lesions without local therapy by the use of Egg Propeptan.

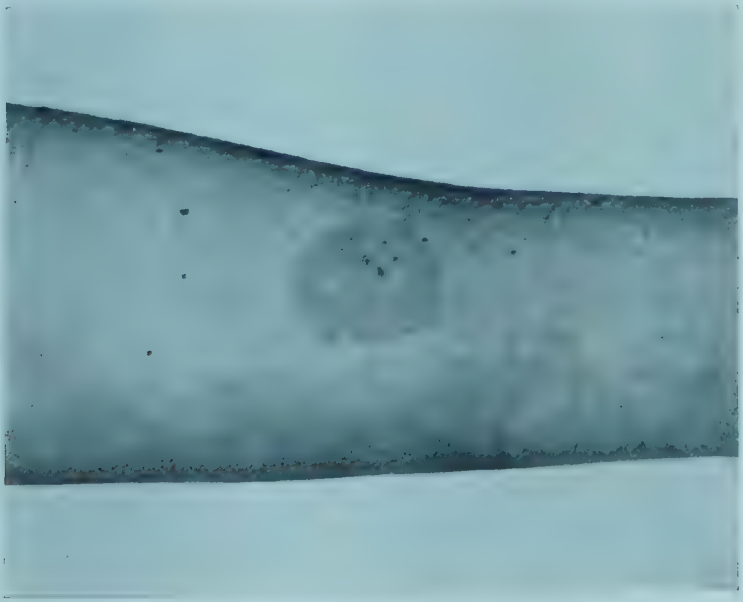

Fig. 115. Passive Transfer of Hypersensitiveness to Egg White by Means of Blood Serum from Patient with Extensive Dermatitis Due to Egg

"Eczematous" reaction appearing after twenty-six hours made up of numerous minute papules and pin-point-sized vesicles. Subjectively there was intense pruritus. Histologic examination (Fig. 116) revealed all the features of a dermatitic reaction (spongiosis of the epithelium, edema of the papillary layer, and leukocytic infiltration around the papillary vessels).

The therapy employed in this case was administration of one egg daily, preceded by Egg Propeptan, for a period of fourteen days. Since neither the pruritus nor the dermatitis reappeared, the patient was given egg without Propeptan in small quantities, slowly increasing from one tenth of an egg to two eggs daily. When the patient was re-examined six months later, she was able to eat eggs and was completely free of symptoms.

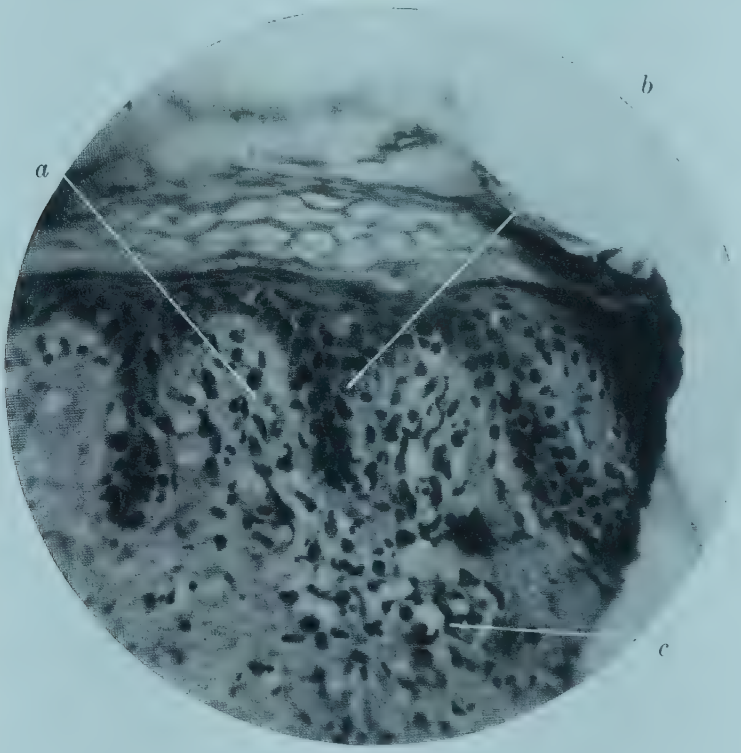

FIG. 116. PHOTOMICROGRAPH OF "ECZEMATOUS" REACTION TO PASSIVE TRANSFER
Same case as in Fig. 115. (*a*) Spongiosis, (*b*) edema of papillary body, (*c*) perivascular infiltration.

Another noteworthy case is that of a 37 year old man who, for ten years, had been suffering from a recurrent oozing dermatitis (Fig. 117), apparently in association with jaundice of long duration. The skin condition always became definitely worse when he was constipated and especially after eating meat, particularly pork, at such times. In view of the marked eosinophilia (11 per cent), he was given treatment designed to correct the intestinal irregularity, and was also put on a Propeptan diet. As a result, the skin manifestations, which had resisted the usual local treatment, promptly showed improvement. On different days the patient ate veal, beef, and pork, ingestion of any of which invariably elicited intense itching and an oozing dermatitis. However, the same quantities of these meats, preceded by 2 or 3 specific Propeptan capsules, were tolerated perfectly, except for slight subjective complaints after eating pork. Intracutaneous tests with extracts of all the meats were entirely negative. On the other hand, passive transfer with pork extract as the antigen was successful, by both the Prausnitz-Küstner and the Urbach-Koenigstein methods. It is, however, interesting to note that the Prausnitz-Küstner reaction was positive only after twenty-four hours.

Finally, we may mention the case of a boy of 3 years whose dermatitis (Fig. 118) began to improve only after we had found horse meat, eaten in the form of sausage, to be the responsible allergen. The discovery was made by means of the Propeptan method. Elimination of this food from the patient's diet was followed by cure.

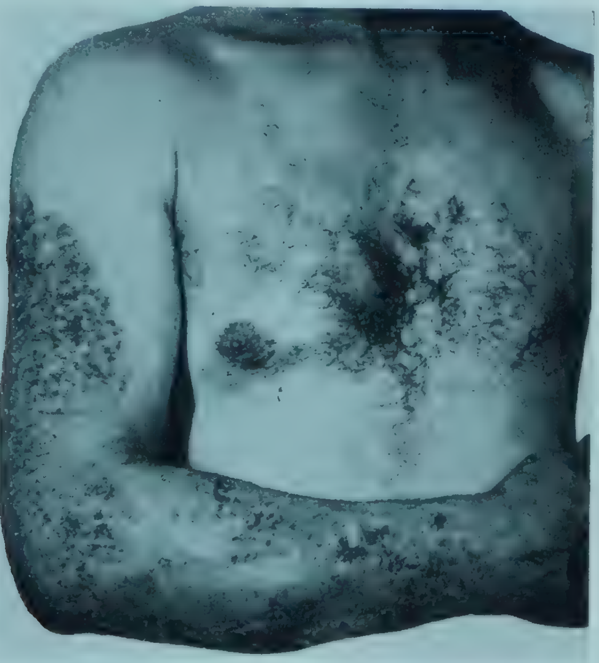

FIG. 117. RECURRENT WEEPING, CRUSTED DERMATITIS DUE TO HYPERSENSITIVENESS TO BEEF
Skin manifestations were controlled with Beef Propeptan

However, a nutritive dermatitis is by no means necessarily always due to animal or vegetable protein. The present writer has encountered several cases in which it was possible to demonstrate that table salt and various spices were the allergizing agents.

2. ALLERGIC DERMATITIS DUE TO DRUGS

Another but relatively small group of internally caused allergic dermatitides consists of those due to drugs taken by mouth and the numerous cases observed to appear after intravenous injection of arsphenamine, gold, and other drugs.

Peters[870] noted rapid improvement in the skin and general condition of 2 patients with severe exfoliative dermatitis following administration of cystine or cysteine. In the first case some 70 per cent by weight of the protein intake was lost in the desquamated skin. The cystine content of this skin was found to be 3.15 per cent, whereas in scarlet fever patients the cystine content of the desquamated skin averaged 2.9 per cent. It is suggested that patients who are losing large quantities of epithelium due to any cause are liable to suffer from lack of sulfur-containing amino acids. Peters gave his patients 0.25 Gm. of cysteine hydrochloride intramuscularly and 1 Gm. by mouth daily for 3 weeks.

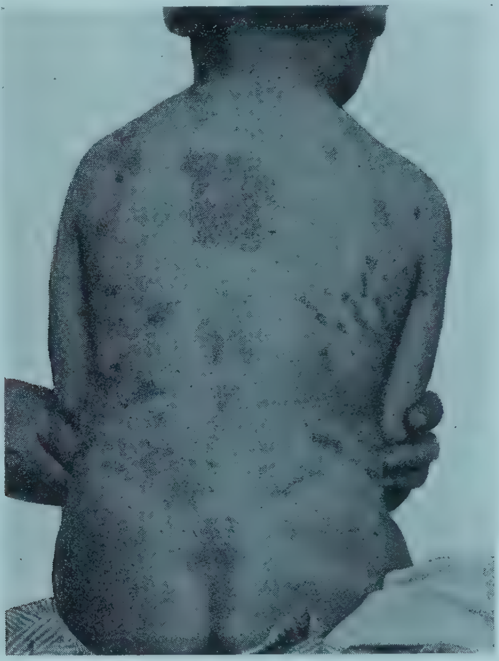

FIG. 118. DERMATITIS DUE TO ALLERGY TO HORSE MEAT

In cases of allergic or toxic drug dermatoses, administration of the responsible drug must, of course, be stopped at once. Moreover, an effort should be made to eliminate the drug through the kidneys by forcing fluids or by evacuating the intestines by means of castor oil and colonic irrigations. In severe cases, such as arsenical exfoliative dermatitis, it is advisable to give quantities of sweetened fruit juices to prevent the loss of glycogen stored in the liver. Daily intravenous injections of 500 cc. of 10 per cent dextrose will also be beneficial. Large doses of ascorbic acid (100 mg. three times daily), vitamin B complex (2 capsules three times daily), or injections of crude liver extract (3 cc. every second day), are likewise indicated here. The results of experiments performed by

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[870] PETERS, B. A.: Lancet 1: 264, 1945.

Voegtlin and associates[97] suggest that proteins should not be withheld in the treatment of patients with toxic reactions to arsenic or gold compounds, because it seems probable that the glutathione or some other sulfhydryl compound in the body tissues might react with the arsenic oxide, for example. This would, of course, reduce the quantity of sulfur in the tissues. This view is upheld by Klauder and Brown's[95] findings that the sulfur content of the skin of patients with arsphenamine dermatitis was the lowest they had encountered in their studies. Since the injection of glutathione is a rather expensive procedure, Klauder suggests the administration of sodium thiosulfate, supplemented with 10 Gm. of glutamic acid daily, plus cystine, which can be obtained by the free ingestion of egg yolk.

During the first few days after the appearance of a severe toxicodermia a period of modified fasting (two or three days on a diet restricted to milk and distilled water) is often beneficial because it gives the eliminative organs a chance to excrete the accumulated toxic products and promote their more thorough oxidation in the body (see page 62).

C. METABOLIC DERMATITIS

This group comprises all dermatitides, acute and chronic, in which some functional disorder or disease of the gastrointestinal tract, the liver, pancreas, kidneys, or of the endocrine glands can be shown to be the principal cause.

The fact that a dermatitis may have its origin in dysfunction or disease of the gastrointestinal tract was discussed at some length in Chapter VI. We recommend that fractional gastric analysis be performed in every case of chronic dermatitis, particularly in those of a nummular character. Ehrmann,[288] Walsh,[743] Ayres, Jr.,[742] Dobreff and Popchristoff,[870] Marchionini,[149] Urbach,[740] and others have noted improvement in dermatitides following correction of demonstrable hypo-acidity or anacidity by administration of hydrochloric acid and pepsin. We recommend relatively large doses, as in the following prescription.

		Gm. or Cc.	
℞	Acidi hydrochlorici diluti	15.0	f℥ ss
	Pepsini	15.0	℥ ss
	Distilled water q.s. ad	180.0	f℥ $\frac{i}{vi}$

Sig. One tablespoonful in one glass of water through a glass tube during meals.

Since chemical and roentgenologic examinations not infrequently prove unreliable, it is advisable, especially in chronic, therapy-resistant cases, to examine the stomach gastroscopically by means of which one can sometimes discover the presence of gastritis and thus be in a position to prescribe etiologic therapy.

Hyperacidity seems to be the underlying cause of dermatitis rather rarely. Thus, Walsh,[743] Marchionini,[149] and the present writer have reported patients with hyperacid levels, whose dermatitis yielded to generous doses of sodium bicarbonate or other antacids.

For therapeutic reasons, in each case it is essential to determine whether the gastric disorder is anatomic or functional, and whether primary or secondary. Furthermore, it is well to bear in mind that in some cases dermatitis and anacidity constitute concomitant expressions of some underlying disturbance of the vegetative nervous system. Lastly, as notably Alvarez[766, 591] and Stokes and Pillsbury[734] have stressed, hypo-acidity and anacidity are not infrequently psychogenic in origin and therefore require appropriate psychosomatic treatment, including the use of sedatives.

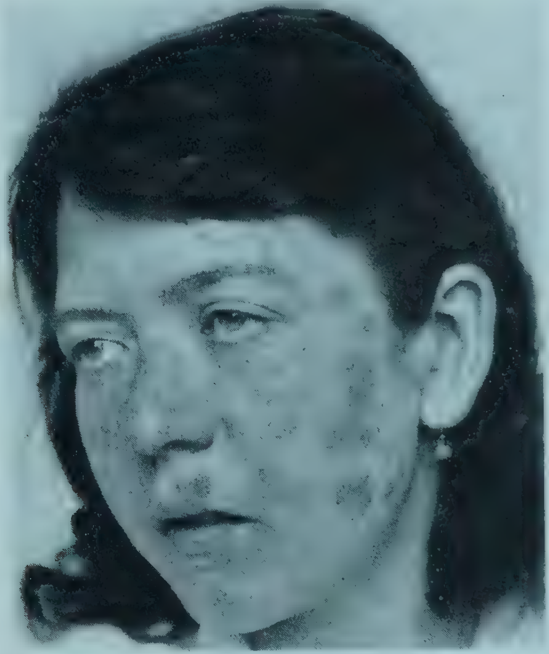

FIG. 119. RECURRENT DERMATITIS ON THE BASIS OF CHRONIC ENTERITIS

When present, and particularly when associated with intestinal disturbances, achylia gastrica may lead to involvement of the pancreatic secretion as well. Fatty stools may be totally absent here, with improper digestion of meat the only evident disorder. A case of this kind was reported by Kauders[847] and is described in some detail on page 345.

There are those cases which, although presenting objective signs of gastritis, fail to respond to the usual therapeutic measures. As Porges[871] has pointed out, under these conditions the possibility of enteritis must be considered, and physical, radiologic, and stool examinations should be

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871. PORGES, O.: Wien. klin. Wchnschr. 44: 442, 1931.

made with this in mind. Very little is known concerning the relationship of enteritis to the etiology of chronic dermatitis. Nevertheless, the writer strongly recommends a trial of the diet described on page 321 in all cases having the symptoms mentioned above. It is to be noted, however, that this regimen must be continued for at least ten days. Hypo-acidity or anacidity if present must of course be corrected as described above. By establishing the presence of an underlying enteritis and treating it effectively, the writer achieved complete cure in a number of instances which had resisted all other therapy for weeks (Fig. 119).

In addition to diseases of the small intestine, disorders of the large bowel sometimes constitute the underlying cause of chronic dermatitis (Fig. 120). Outstanding in this condition are putrefactive and fermentative processes, perhaps through the formation of intestinal toxins; constipation also plays an important role here. Therefore, it is important to bear in mind the possible existence of cecitis and adjacent colitis and of putrefactive dyspepsia and fermentative dyspepsia. For the dietary treatment of these conditions the reader is referred to page 322.

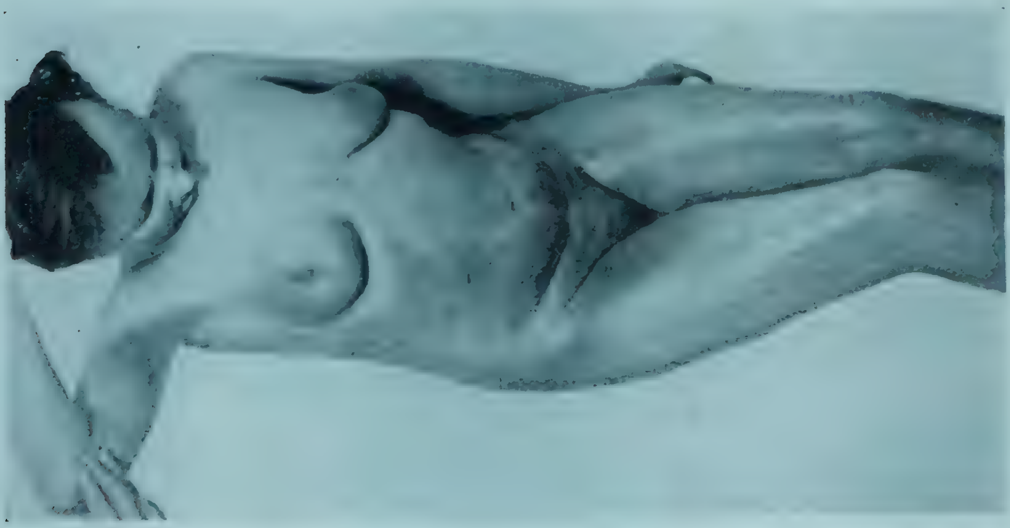

FIG. 120. PERIGENITAL AND AXILLARY DERMATITIS DUE TO INTESTINAL PUTREFACTIVE DYSPEPSIA

Moreover, cecitis may sometimes be concurrent with enteritis, the writer having had occasion to observe one of these cases. Naturally, the physician is unable to institute the proper therapeutic regimen unless he discovers the existence of this combination.

In every case of chronic dermatitis the patient must be closely questioned about constipation, or rather whether he has regular bowel movements without the use of laxatives. Time and again one is surprised to discover how extraordinarily high is the incidence of spastic or atonic constipation among patients with dermatitis. Wherever possible, regular bowel evacuations should be established by dietary measures alone (for details, see p. 321). In the beginning, however, it may be well to give properly supervised high colonic irrigations, particularly in order to eliminate intestinal toxins speedily.

Diabetes mellitus not uncommonly constitutes the underlying cause of dermatitis. A diabetic etiology should be considered especially in cases presenting intertriginous dermatitis (under the breasts, in the crurogenital folds) or dermatitis around the orifices of the body (mouth, anus, urethra, vagina). In cases of this kind one quite commonly finds fungi and yeast in the involved skin areas, probably due to the fact that in diabetes the sweat is abnormally high in sugar and thus creates a terrain favorable to the growth of fungi in the affected areas. Another type of manifestation presents a clinical picture of a more or less diffuse, poorly defined area of reddening and infiltration of the skin, showing in part vesicular, in part papular, efflorescences, and generally accompanied by intense itching (Rost[872]).

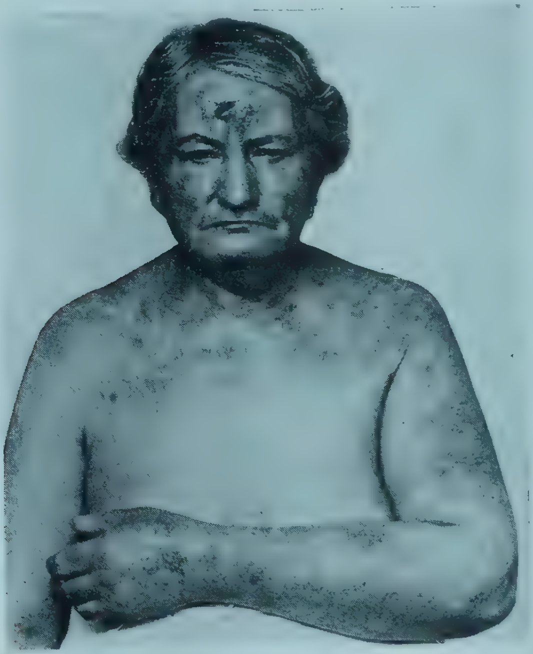

FIG. 121. CHRONIC DERMATITIS OF DIABETIC ORIGIN

The possibility of a diabetic etiology should also be kept in mind in every case of chronic, therapy-resistant dermatitis (Figs. 121, 122). However, in order to determine whether a dermatosis is of diabetic origin, examination of the urine for sugar and determination of the fasting blood sugar level do not by any means suffice. If the latter is normal, a glucose tolerance test must be performed. If this is not feasible and there is reason to suspect disturbed sugar tolerance, we advice placing the patient on a strict diabetic regimen for three or four days and carefully observing the results. This procedure is of great value because, as we have been able to demonstrate,[11] there are some cases of dermatitis in which the curve of the blood sugar tolerance test is normal and only the fasting skin sugar level or the skin sugar tolerance test reveals the presence of a disturbance of carbohydrate metabolism. In our opinion, this view is confirmed by the fact that the dermatitic lesions of these patients disappear completely on a diabetic diet plus small doses of insulin, only to reappear promptly when the previous high carbohydrate diet is resumed.

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[872] ROST, G. A.: Deutsche med. Wchnschr. 55: 173, 1929.

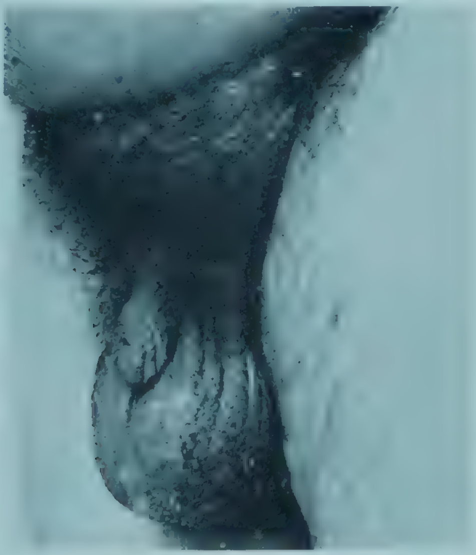

FIG. 122. CHRONIC SCROTAL DERMATITIS DUE TO DIABETES

Thus, the writer observed the case of a woman, aged 56, with extensive weeping dermatitis on the inner aspect of both thighs, reaching up to the natal cleft. There was no sugar in the urine. The fasting blood sugar level was normal, and the blood sugar tolerance curve showed a peak of 185 mg. with a hypoglycemic level at the end of three hours. In short, there was no definite clinical evidence of diabetes. Nevertheless, diabetic treatment led to prompt retrogression of the cutaneous manifestations, which had previously been most refractory to treatment.

Such cases are not to be confused with those in which there is hypersensitiveness to carbohydrates, a state which the writer has observed in some instances of chronic dermatitis. Patients with carbohydrate allergy can readily be distinguished from those with latent diabetes by the fact that the former respond favorably to a low carbohydrate diet and are intolerant of even small doses of insulin.

Lastly, as Escudero[873] has reported, there is the type of dermatitis in which the disturbance of carbohydrate metabolism is only moderate, while hyperlipemia is pronounced. In these cases, according to Escudero, the dermatosis yields to a diet very low in fat and high in carbohydrates plus the administration of insulin. It is interesting to note that a high carbohydrate, relatively low fat diet is now being extensively used in the management of diabetes.

For a presentation of the dietary management of diabetes see page 89.

While diabetes mellitus is now generally recognized as an etiologic factor in dermatitis, the question as to whether gout can be the cause of dermatitides is still highly controversial. Most authorities are inclined to doubt this. On page 107 we cited a few reports of isolated cases of dermatitis which had been refractory to local treatment for years and which finally yielded quite promptly to a strict gout diet. Kreibich[874] has the impression that pruritus, lichenification, and dry facial dermatoses are quite commonly encountered in patients who have suffered genuine attacks of gout. Schamberg and Brown[875] found that cases of generalized, and particularly of erythematous, forms of dermatitis showed high uric acid levels in the blood and sometimes also abnormally high nonprotein nitrogen and urea levels. They noted an improvement in the cutaneous condition on a purine-free diet in the case of generalized dermatitis, and following a low protein diet in the erythematous type. However, high uric acid levels alone do not warrant the diagnosis of gout, even after a few days on a purine-free diet. We have been able to demonstrate[11, 135] that the uric acid content of the blood and tissues of individuals with dermatitis can be increased at will by any kind of nonspecific local irritation. The presence of a gouty diathesis may be definitely established in a given case only if the purine tolerance test with 10 Gm. sodium nucleinate is followed by delayed purine excretion in the urine, so characteristic of gout, with a simultaneous exacerbation of the dermatosis. Description of the dietary management of gout may be found on page 108.

From investigations of the past few years it seems highly probable that diseases of the liver may be involved either directly or indirectly in the production of dermatitides. Disturbances of the hepatic excretory function (i.e., the secretion of bile) may be relevant in this connection. Indeed, a number of authors (Smithies,[774] Schur,[794] Menagh,[795] Goss,[796] Daniel,[797] Shay and collaborators,[798] Hansen-Pruess[799]) have reported marked improvement in cases of severe dermatitis following regular nonsurgical biliary drainage, by stimulation of the flow of bile by magnesium sulfate or following cholecystectomy. By means of the last procedure, Urbach and Shay[800] achieved a permanent cure in a severe case of hypersensitiveness to light. Among these potentially causal hepatic factors the most important are the disorders of metabolic processes within the liver, which are concerned with the detoxification of poisons coming from the intestine (Lortat-Jacob[876]), and those concerned with the regulation of the normal metabolism of the basic foodstuffs. A number of authors (Rocchini,[801] Kordowich,[802] Guldberg and Hannisdal[803]) have encountered an especially high incidence of hepatic dysfunction in dermatitides of otherwise undetermined origin. Marquardt's[804] studies would seem to show that metabolic disorders of the liver constitute a great obstacle to the cure of chronically recurrent dermatitides. Larat and Siebenmann found that a number of their patients presented marked urobilinuria while others showed a great increase in urobilinogen. These abnormalities disappeared when the dermatitis cleared up. The French authors regard these substances not as the direct cause of the cutaneous disease but rather as signs of a hepatic disturbance through which the noxious substances are produced. Figure 123 shows a generalized dermatitis of eighteen months' duration in a woman of 36. This condition had resisted all forms of therapy until the presence of hepatic disease was demonstrated by liver function tests and controlled by liver injections and proper diet (see p. 338). Urbach[788] demonstrated that hepatopathy, associated with dysbacteria and porphyrinopathy, is involved in the etiology of certain dermatitides due to photosensitization. Barber and Oriel[751] have reported gratifying results with a liver-sparing diet in certain cases of dermatitis. The present writer favors this dietary approach and feels that it should be supported by a combination of insulin and high carbohydrate therapy (50 Gm. of dextrose orally plus 10 to 15 units of insulin at the same time, twice daily).

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[873] ESCUDERO, P.: Ref. sud-am. de méd. et de Chir. (Paris), **1:** 1097, 1930.

[874] KREIBICH, K.: Ekzeme und Dermatitiden; in Handb. f. Haut- u. Geschlechtskr. ed. by J. Jadassohn. Berlin: Springer, 1927.

[875] SCHAMBERG, J. F. and BROWN, H.: Arch. Int. Med. **32:** 203, 1923.

It should be noted that, in many cases of toxic dermatitis due to drugs (e.g., arsphenamine or gold), the cutaneous and the hepatic injuries constitute concomitant expressions of an underlying toxic cause. As discussed in some detail on page 341, liver damage may be the consequence of extensive dermatitides.

In concluding this section, we shall briefly mention nummular dermatitis. This term denotes coin-shaped erythematous patches studded with small vesicles or papulovesicular lesions chiefly located on the dorsa of the hands and fingers and the extensor surfaces of the upper and lower extremities. Gross[877] considers this form of dermatitis to be a clinical entity and believes that asteatosis of the skin is its chief predisposing cause.

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[876] Lortat-Jacob: Clinique et Laboratoire. No. 6, Sept. 20, 1923.

[877] Gross, P.: Arch. Dermat. & Syph. **44:** 1060, 1941.

Since asteatosis is often an early sign of vitamin A deficiency, he tried large doses of this vitamin (75,000 U.S.P. units daily, followed later by a maintenance dose of 25,000 units) and reported favorable results. The local treatments consist of simple topical medication. In addition, it is important that the use of soap and water, including bathing, should be strictly prohibited.

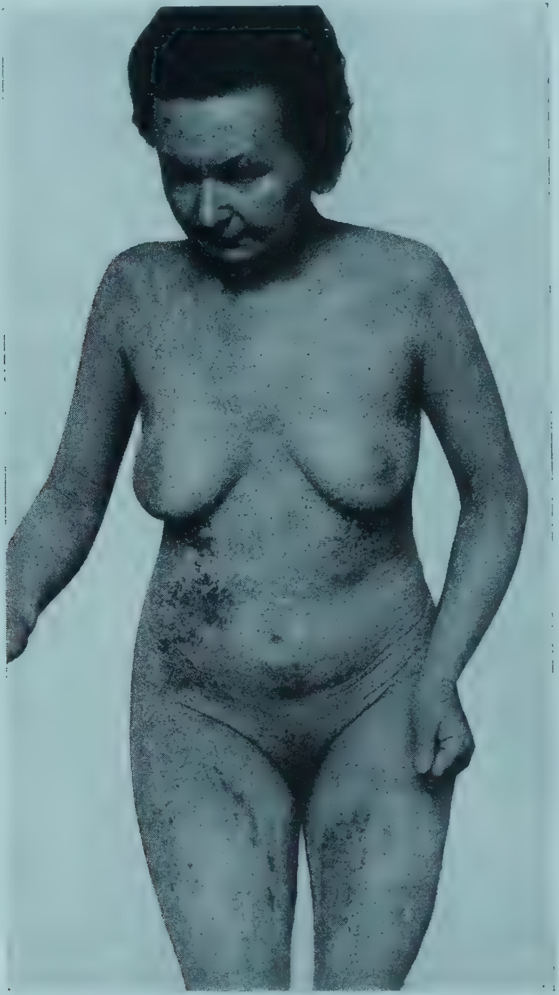

Fig. 123. Dermatitis on the Basis of Liver Disease

Case of a 36 year old woman suffering from generalized dermatitis for eighteen months. This was resistant to all forms of therapy until liver disease was discovered by liver function tests and treated by diet and insulin.

D. NEURODERMATITIS

For clinical, pathogenetic, and therapeutic reasons, a distinction must be made between the dermatitides described above and that form to be referred to below as neurodermatitis. This condition is in turn to be divided into two subgroups: the circumscribed type (also called neurodermatitis circumscripta chronica, lichen simplex chronicus of Vidal), and the disseminated type (also known as atopic dermatitis of Sulzberger,[852] generalized neurodermite of Brocq, eczema-asthma-hay fever complex of Stokes,[878] prurigo diathesique of Besnier, and flexural eczema).

Symptomatology

Circumscribed neurodermatitis is characterized by sharply defined, highly lichenified, infiltrated, hyperpigmented (though in rare instances depigmented), intensely pruritic lesions showing a tendency to recur. The sites of predilection are the back and sides of the neck, the dorsum of the hand, the medial aspect of the lower leg. This form of dermatitis is practically never encountered in children.

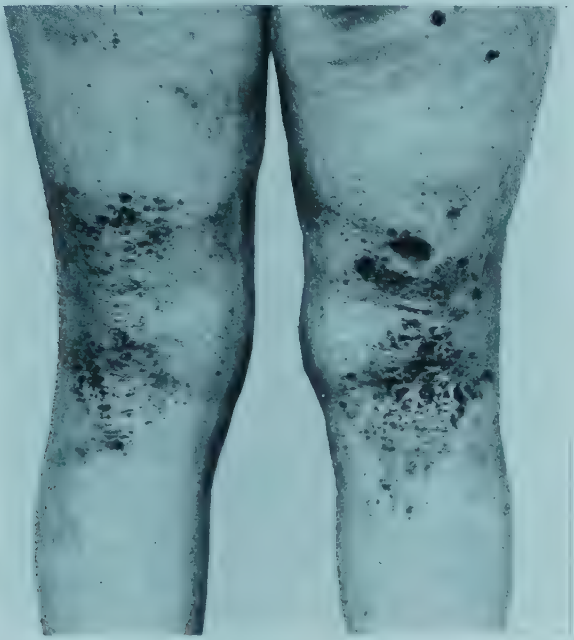

FIG. 124. NEURODERMATITIS LOCALIZED IN THE POPLITEAL SPACES

Disseminated neurodermatitis is almost invariably located on the face and on the flexural surfaces of the principal joints, particularly the antecubital and popliteal spaces (Fig. 124), and less commonly in the inguinal, crural, and axillary folds. In cases of many years' duration, the skin of the face may become thickened and leathery from lichenification, with a color ranging from grayish to brownish purple, thus producing the appearance of a ghostly mask; moreover, the characteristic absence of eyebrows, at least laterally (due to rubbing), giving the face an odd expression, so that most neurodermatitis patients look more or less alike.

In both the disseminated and circumscribed types, the primary lesion

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878. STOKES, J. H.: Med. Clin. North Amer. 15: 279, 1931.

usually consists of a skin-colored papule, the center of which is often covered with a bloody crust as a result of scratching due to intense pruritus. The papules, particularly those in the flexures and on the medial aspect of the thigh, become confluent and form poorly defined plaques; this eventually gives the skin its characteristic coarse appearance. The condition may become secondarily impetiginized, owing to scratching and superimposed infection. Finally, generalization of the skin manifestations may take place in patients of all ages. The itching in these cases is unbearable and is often relieved somewhat only when the skin bleeds as a result of vigorous scratching. Stokes calls attention to the fact that the skin of these patients turns white instead of red upon rubbing or scratching (white or sympathicotonic dermographism).

Finally, it should be pointed out that neurodermatitis, particularly in childhood, is very often a direct continuation of infantile dermatitis, chronologically and probably also pathogenetically. At first only the flexures are involved; then, approximately in the eighth to tenth year of life, the child begins to present the typical picture of neurodermatitis disseminata, with the characteristic involvement of the face. Only rarely do the cutaneous manifestations of neurodermatitis make their first appearance after puberty. In these cases, as well as in those dating back to early childhood, the entire skin is invariably strikingly dry and strangely brownish gray in color.

Pathogenesis

The pathogenesis of neurodermatitis is by no means uniform, nor is the condition necessarily of strictly allergic origin. The term "neurodermatitis" seems to us to be preferable to all other designations, since it most clearly emphasizes the fact that an unstable nervous system, overreacting to emotional strain, plays a special role in this skin disease, including the numerous cases in which a food or an inhalant can be shown to be the causal allergen. Moreover, this does not in any way negate the fact that heredity is often an important predisposing factor in the causation of neurodermatitis.

While in contact dermatitis the epidermis is the shock structure, in neurodermatitis the blood vessels of the cutis are the shock organ. In other words, we are dealing here with a vascular-cutaneous hypersensitiveness. This serves to explain the fact that neurodermatitis is very frequently associated with vascular hypersensitiveness in other organs, as in asthma, hay fever, and migraine.

In a small number of cases it is possible to demonstrate by the patch test method that the neurodermatitis is due to some contactant. Inhalants, however, are far more commonly responsible for causing and maintaining neurodermatitis. In these cases the allergen is transported to the shock structure by the hematogenous route.

In another group of cases, the principal cause of neurodermatitis was found by the writer to be hypersensitiveness to foods. Most of the patients in the group were children, (Figs. 125, 126) but a number of adults were also included. The most commonly encountered allergens were eggs, milk, flour, fish, and meat. The diagnosis was established by the elimination and trial diet methods.

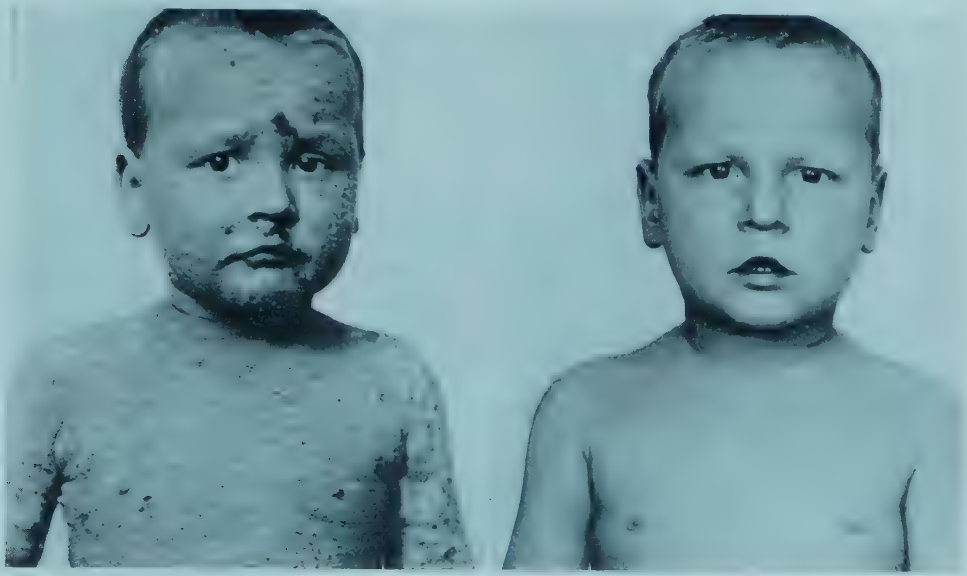

Fig. 125 Fig. 126

Neurodermatitis in a 3 Year Old Child Due to Egg Allergy

Fig. 125. Appearance before treatment.

Fig. 126. After three weeks of strict elimination of eggs.

However, for every one of the relatively few cases in which it is possible to identify the cause of neurodermatitis, there are dozens in which the causal agent cannot be found.

The question of the importance of endogenous allergens originating in faulty digestion, endocrine dysfunction, and other metabolic disorders has not received adequate study. As a result, there is, in the writer's opinion, a marked tendency to underestimate the influence of endogenous allergens in this connection. We believe that they are of considerable importance and that this will eventually be recognized.

The influence of predisposing factors is perhaps greater in neurodermatitis than in any other allergic disease. Every physician knows that neurodermatitis is somehow dependent, for example, upon seasonal influences, in that the condition often flares up in the spring and fall. It is not yet known to what extent these exacerbations are dependent upon disturbances of the endocrine functions or imbalance of the sympathetic-parasympathetic equilibrium. There are numerous indications that at these times of the year the irritability of the vegetative nervous system is increased or a hyperthyroid state is present. Furthermore, mention must be made here of the significance of gastrointestinal disturbances (hypoacidity, abnormality of intestinal flora, constipation) and of infections (foci in the teeth, tonsils, gallbladder, and in the pelvis of the kidney).

A few examples may serve to illustrate the widely varied causes of neurodermatitis. They will also show that, although food allergy certainly plays an important role, certain predisposing factors are necessary to pave the way for oral allergization. Psychic and psychosomatic influences are of special significance in this connection.

Case 1. A trained nurse whose mother was hypersensitive to strawberries (urticaria) developed weeping, dermatitic skin manifestations about the elbows in infancy. The lesions recurred frequently and, from her fifteenth year on, also involved the neck. At the age of 26, following copious consumption of eggs (from 2 to 4 daily, including one raw egg), generalized neurodermatitis (Fig. 127) made its appearance and did not retrogress appreciably until eggs had been eliminated from the diet. When the patient was first seen, she presented neurodermatitis on and about the forehead, the eyelids, the throat, the nape of the neck, and the elbows. There were positive cutaneous reactions to yolk of egg, white of egg, and peas. Stroking of clinically normal skin evoked no response, but affected skin areas reacted with definite urticarial inflammation and severe itching. Ingestion of a soft boiled egg was followed in ten minutes by severe itching of the neck and face and in the antecubital spaces, and shortly thereafter urticarial erythema appeared in these areas. At the same time, the patient complained of severe headache and of an uncontrollable urge to yawn; and some thirty minutes later there was vomiting followed by diarrhea; in short, all the signs of "anaphylaxie alimentaire."

The hypersensitiveness was of such a high degree that oral administration of 1 mg. of chicken protein, as well as intracutaneous injection of a 1:10,000,000 dilution of egg white, sufficed to evoke itching and erythema on and about the forehead, cheeks, neck, and elbows. Passive transfer of the hypersensitiveness by the Prausnitz-Küstner method resulted in an urticarial wheal 1.5 cm. in diameter surrounded by a 3 cm. halo of reddening.

Systemic hyposensitization by the intracutaneous route was attempted. However, since a 1:600,000 dilution again evoked a strong focal reaction, oral hyposensitization was tried, beginning with 1 mg. of egg white. After fourteen days of systemic administration of egg white and egg yolk, the patient had been completely hyposensitized by mouth (Fig. 128). On discharge she was able to eat a half an egg without suffering any objective or subjective symptoms. However, four months later all the symptoms recurred.

Case 2. A 27 year old patient had been suffering from disseminated neurodermatitis since the age of 4 years. She knew that she must not eat eggs because they produced nausea. Accidental contact with egg such as occurred in the kitchen, for example, when she happened to touch her eyelids with fingers that had been spattered with white of egg, evoked marked local swelling and severe itching of the neurodermatitic skin within ten minutes (Fig. 83, p. 263) while the clinically normal skin areas presented no reaction whatever. Introduction of a drop of egg white into the conjunctival sac brought about pronounced conjunctival injection with narrowing of the eyelids, lachrymation, and coryza. Administration of Egg Propeptan served to inhibit these manifestations completely (Fig. 84, p. 263). Ingestion of a small quantity of raw egg white brought on severe anaphylactic shock. Treatment consisted of oral hyposensitization, beginning with 1 cc. of a 1:1,000 solution of raw egg white, equivalent to 1 mg. of protein. When the patient was able to tolerate 5 Gm. of raw egg protein, the skin became soft and the itching disappeared. However, there was a recurrence of the cutaneous manifestations a few months later.

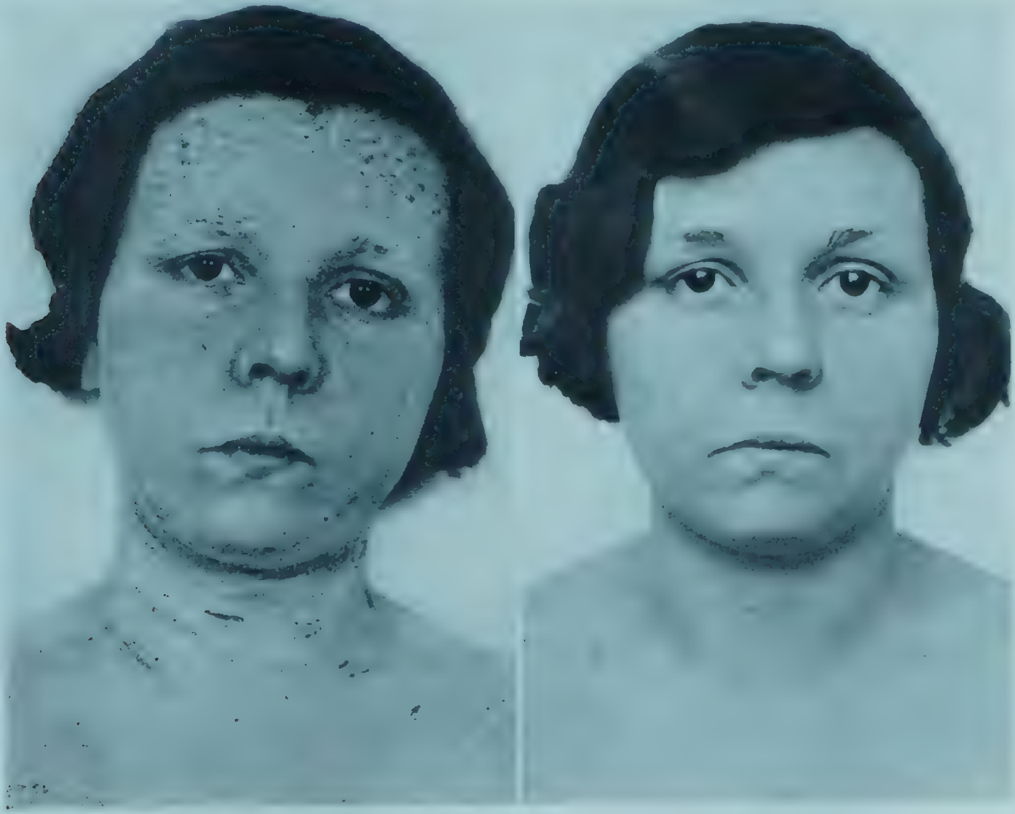

FIG. 127 FIG. 128

NEURODERMATITIS DUE TO HYPERSENSITIVENESS TO EGGS

FIG. 127. Before treatment.

FIG. 128. After oral hyposensitization with egg.

Positive skin reactions are not always of etiologic significance for diagnostic purposes, nor can a positive passive transfer test for hypersensitiveness be automatically accepted at its face value. Positive skin reactions and successful passive transfers may be considered significant in the etiopathogenetic sense only if cutaneous or oral administration of the incriminated food evokes the objective and subjective symptoms of neurodermatitis, and if these symptoms disappear when contact with the excitant is terminated.

There has been reported unquestionable hypersensitiveness to such foods as milk (Hasen[illegible]), egg (Blumenthal and Jaffe,[879] Wysocki[880]), wheat flour (Gutmann[illegible]), and fish (Boss[illegible]). Alimentary hypersensitiveness to cocoa has also been demonstrated in a patient with neurodermatitis circumscripta, in whom the skin disease was cured by elimination of this food from the diet (Samek[881]).

It is interesting to note that, in one case of neurodermatitis, the writer was able to demonstrate the presence of skin diabetes.

Case 8. A patient, aged 40, had been suffering from typical neurodermatitis of the face, forearms, and legs for thirteen years. He stated that the skin manifestations were regularly exacerbated by consumption of large amounts of carbohydrates and showed definite improvement when the diet was free from such foods. Table 79 shows that the blood sugar curve was perfectly normal but the skin sugar curve pathologic, since the skin sugar-blood sugar ratio was 71 per cent to begin with and as high as 82 per cent five hours later. The sugar tolerance test also provoked objective and subjective exacerbation of the skin manifestations. Insulin therapy, combined with a low carbohydrate diet, served to control the dermatitis.

TABLE 79.—*Skin Sugar and Blood Sugar Tolerance Curves in a Case of Neurodermatitis on Basis of Skin Diabetes*

Time	Skin Sugar	Blood Sugar
fasting	68	97
1 hour after sugar meal	89	134
2 hours " " "	83	129
3 " " "	77	125
4 " " "	77	92
5 " " "	78	97

In still other instances, gastrointestinal disturbances have been found to play an important role. Many of the writer's neurodermatitis cases exhibited either gastric anacidity or hypo-acidity; in about 30 per cent of these, roentgenologic examination disclosed the presence of hypersecretion. The latter is evidence of irritation of the mucous membrane itself or of a heightened reaction on the part of its blood vessels to some excitant. It is now known that hypersecretion may sometimes accompany gastric hypo-acidity.

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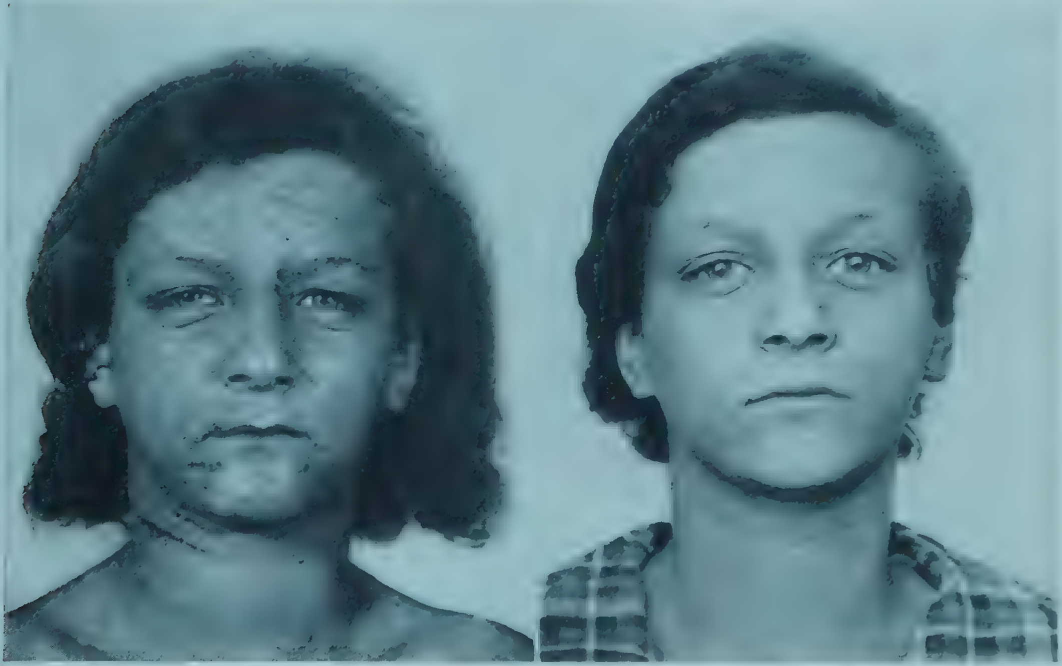
879. BLUMENTHAL, F. and JAFFE, K.: Ekzem und Idiosynkrasie. Berlin, Karger, [illegible]

880. WYSOCKI, K.: Arch. f. Dermat. u. Syph. 166: 616, 1932.

881. SAMEK, J.: Dermat. Wchnschr. 100: 59, 1935.

A number of different methods are employed to determine the causal allergen. If the manifestations abate during the patient's stay in an allergen-free room, it may well be assumed that the allergen is an inhalant. Further investigations will then have to be undertaken to ascertain its identity, for example, silk, feathers, or dust. If food is suspected of being the allergen, a strict elimination diet must be instituted. Skin tests, especially by the intracutaneous method, are in general of no clinical significance. Positive skin reactions and successful passive transfer tests are diagnostically significant only if external application or internal administration of the suspected allergen causes the objective and subjective symptoms of neurodermatitis to appear, and if these lesions disappear on elimination of the agent. Lastly, it must be mentioned that a negative skin test by no means rules out the possibility of food allergy.

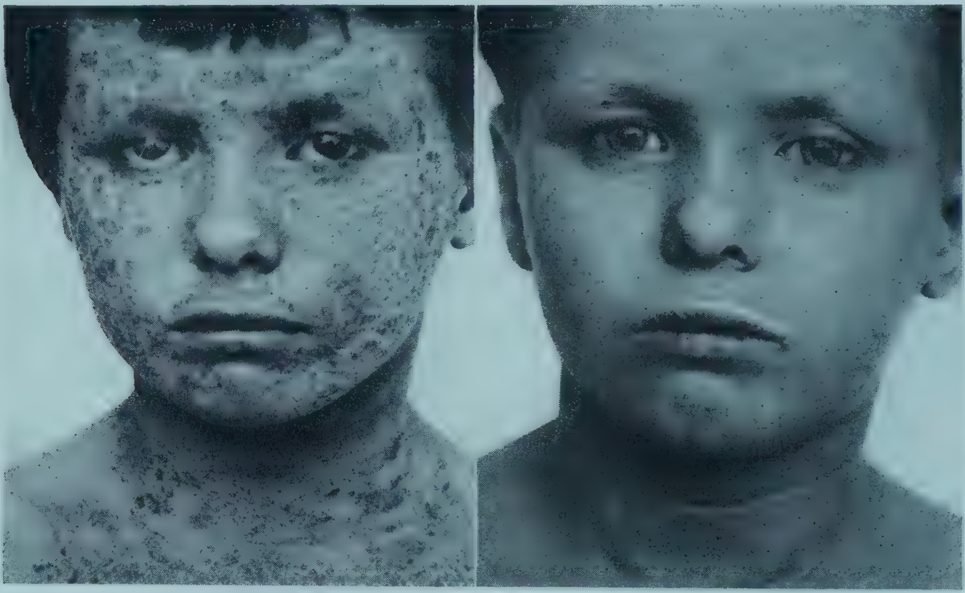


NEURODERMATITIS AND ASTHMA DUE TO HYPERSENSITIVENESS TO MILK AND FEATHERS
FIG. 129. Appearance before treatment.
FIG. 130. Same patient two weeks after strict elimination of milk and feathers.

Therapy

Neurodermatitis is a disease that tries the skill and patience of the allergist and the dermatologist alike. Since the condition is generally brought on by three principal factors—(1) inhalant, contact, or food allergens, (2) certain predisposing factors, and (3) an unstable nervous system overreacting to emotional strain—all must be corrected and, so far as possible, removed at the same time. Hospitalization is advisable in order to facilitate the efficient performance of all necessary environmental, dietary and skin tests.

The specific treatment depends, naturally, on the identification of the specific agent. When there is hypersensitiveness to a contactant, inhalant, or ingestant, exposure to the agent must be eliminated or appropriate hyposensitization measures attempted. This may be accomplished with fairly good results when the causative allergen is dust, silk, feathers, or fungus spores. Removal of these allergenic substances from the patient's environment is of paramount importance (Figs. 129, 130).



Effect of Raw Food Diet in a Case of Neurodermatitis
Fig. 131. Appearance before treatment.
Fig. 132. After four weeks of raw food diet.

The management of nutritive allergy in children is discussed on p. 384. The writer has obtained satisfactory results with the propeptan method in cases of this type. In other instances, we found the raw food diet as introduced by Schiff[881a] to be of definite value (Figs. 131, 132).

Predisposing factors, such as gastrointestinal and endocrine disturbances as well as focal infections, should be eliminated as carefully as possible. In almost all cases of neurodermatitis the physician is obliged to apply psychotherapy, ruled by good common sense and directed as much to the patient's family and friends as to the patient himself. The chief purpose of psychotherapy is to lower nervous reactivity. This is accomplished by means of recreation, hobbies, change of environment, particularly a sojourn at the seashore, with frequent bathing and sun baths, or ocean voyages. Among the drugs, Bellergal (½ or 1 tablet three times a day) and Calcibronate granules (1 teaspoonful three times a day) have proved to be the most useful.

[881a] Schiff, E.: Deutsche med. Wchnschr. 58: 882, 1932.

Cases in which a specific cause cannot be found or which are refractory to specific treatment must be treated symptomatically. This approach may be divided into local and general measures. Topical dermatologic treatment is of the utmost importance. First of all, the use of soap and water, including bathing, is strictly forbidden. However, ocean baths are an exception to this rule, for they are definitely beneficial when combined with exposure to sunlight. Cold compresses with 2 per cent resorcin, 3 per cent boric acid, or 0.25 per cent aluminum acetate will provide relief from enervating itching. If the skin is very dry, owing either to slight ichthyosis or to previous x-ray treatment, it should be covered with gauze spread with the following cold cream before the compresses are applied

	Gm.	
Boric acid	0.2	gr. iii
Greaseless base	60.0	℥ ii
White petrolatum	100.0	q.s. ad ℥iii

Lotions and ointments used should be free of lanolin, since many neurodermatitis patients are allergic to animal fat. Lotions should contain enough oil to make the skin supple. For example:

	Gm. or Cc.	
Olive oil	20.0–40.0	f ʒ v – x
Zinc oxide		
Talc	aa. 20.0	aa ʒ v
Glycerin		
Water	aa. 30.0	aa q.s. ad f℥i

To ointments there should be added tar, particularly naftalan or naftex (Lascoff), crude coal tar, or oil of cade:

	Gm. or Cc.	
Crude coal tar	3.0–10.0	ʒi–iii
Sesame oil	10.0	f ʒ iii
Zinc oxide		
Talc	25.0	aa ʒ vi
Petrolatum	120.0	q.s. ad ℥ iv

X-ray treatment definitely helps to overcome the itching; it should be used sparingly, however, since it dries the skin, thus initiating a vicious cycle.

Systemic measures include fever therapy with bacterial vaccines, such as typhoid vaccine or pyrifer. Because of the danger of anaphylaxis, milk injections are not recommended. Good results are often obtained nonspecifically by a complete change of diet, for example, a regimen consisting exclusively of a raw fruits and vegetables for from two to four weeks. The favorable influence of a change of climate (seashore or mountains) has been mentioned above. It must be borne in mind, however, that the relief obtained from these nonspecific measures cannot be expected to persist for more than a few weeks, unless in the interim the allergenic agent and the predisposing factors are discovered.

E. INFANTILE DERMATITIS (INFANTILE ECZEMA)

Although it is often extraordinarily difficult—in fact, sometimes impossible—to differentiate between infantile and seborrheic dermatitis, for therapeutic reasons every effort should be made to do so in each case.

Symptomatology

Infantile dermatitis is characterized by poorly defined areas of acute, subacute, or chronic inflammation of the skin, consisting of erythematous papulovesicular primary lesions, with intense itching. In the majority of cases, infantile dermatitis ends in a spontaneous cure when the child reaches the age of about 2 years; it may recur now and then, usually much later in life, in the form of some other type of dermatitis. Many of these patients sooner or later present other allergic manifestations, particularly asthma. However, in a small minority of cases the cutaneous manifestations continue throughout childhood and even into adult life, though they gradually assume a different character, presenting the typical picture of localized or disseminated neurodermatitis. This is observed not only in children in whom the skin disease has been accompanied by asthma from earliest youth, but also in unusually severe and refractory cases. While infantile dermatitis occurs chiefly in the so-called exudative type (Fig. 133), it is occasionally seen also in overfed (Fig. 134) and atrophic (Fig. 135) children. As a rule, the skin of infants of the first type is not firm and taut as is usual in overfed children, but flabby and flaccid in appearance and on touch. Adolf Czerny assumed that the condition is due to a metabolic disturbance, for which he coined the designation "exudative diathesis." When dressed or when covered up in bed, these children give an initial impression of being fat and overfed; undressed, however, they typically present strikingly thin thighs and legs.

The characteristic primary lesion is a small exudative papule which may become a vesicle or be topped with a crust if the overlying epidermis is removed by scratching. The clinical manifestations begin with symmetric dermatitic lesions in both cheeks—the so-called milk crusts (Fig. 136). This phase is replaced in turn by a very intensely pruritic, usually excoriated and crusted vesiculation on an acutely inflamed base (Fig. 137).

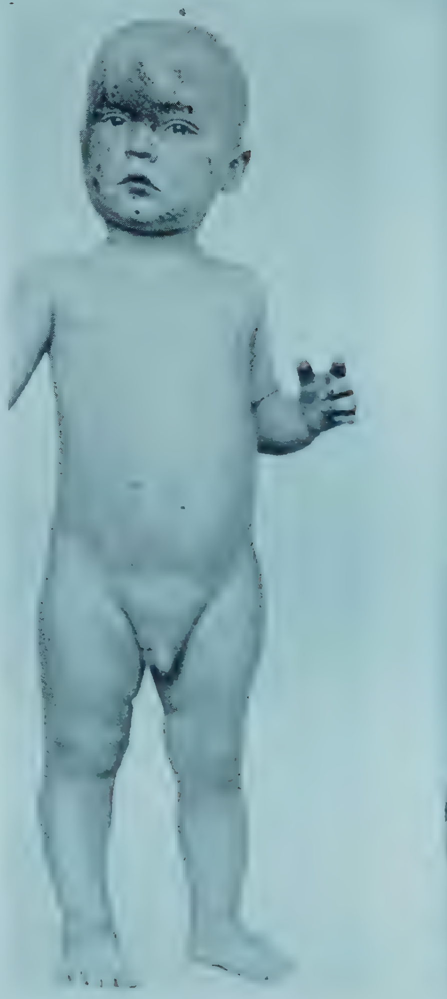


FIG. 133

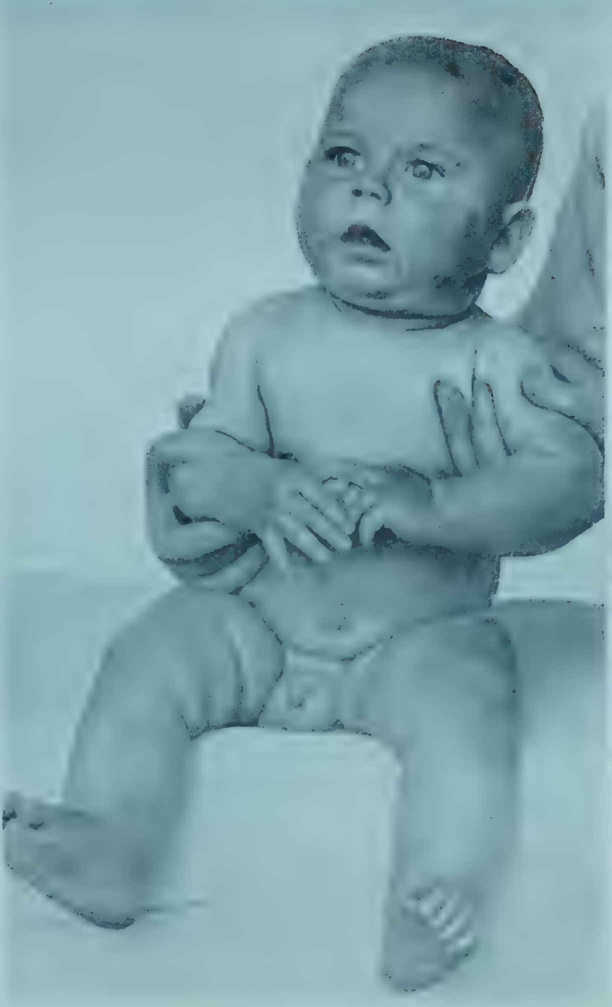


FIG. 134

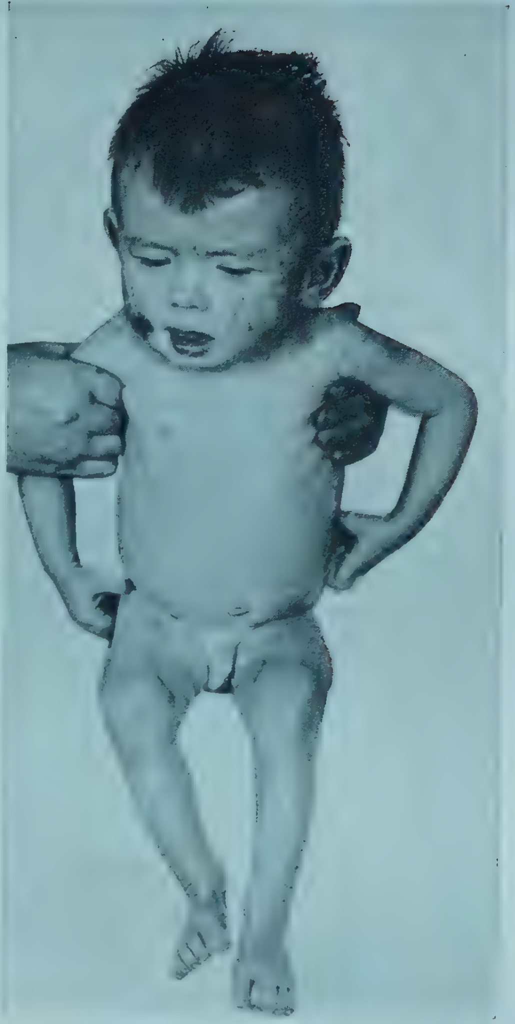


FIG. 135

THE THREE CONSTITUTIONAL TYPES OF CHILDREN WITH INFANTILE DERMATITIS

FIG. 133. Exudative diathesis (Czerny). Note difference between pasty face and relatively thin legs.

FIG. 134. Overfed type.

FIG. 135. Atrophic, undernourished type.

These exudative lesions obviously offer a terrain highly suitable for bacterial growth and, in fact, very frequently lead to a secondary pyogenic infection (Fig. 138) with lymphadenopathy. But even at this time the patient usually presents the characteristic pallor of the face.

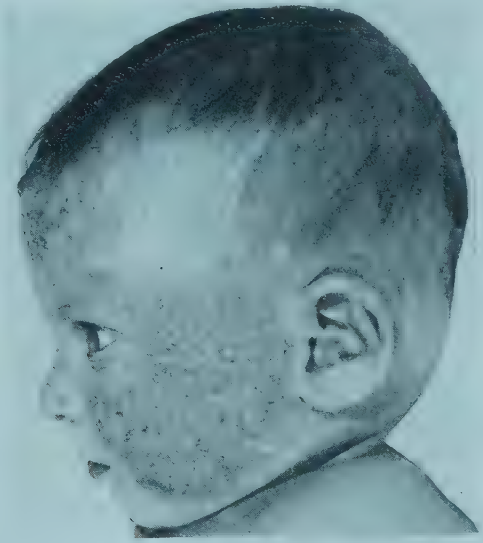


FIG. 136. INFANTILE DERMATITIS. DRY FORM: "MILK CRUST"

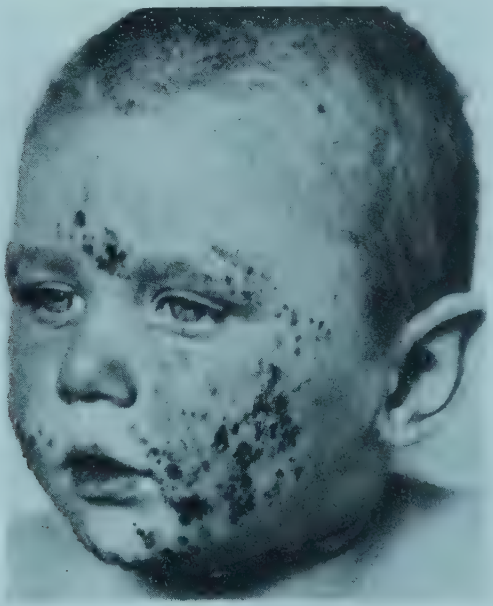


FIG. 137. INFANTILE DERMATITIS. EXUDATIVE FORM

The papulovesicular eruption tends to spread after a while to other parts of the body, chiefly to the forearms, and the outer aspects of the lower portions of the legs. Not infrequently, other areas may also be extensively involved. The clinical manifestations are manifold: erythema, papules, vesicles, crusts, scales, and even wheals may exist side by side.

Pathogenesis

Today there is no doubt that infantile dermatitis is the expression of an allergic reaction of the body. The only controversial question is the extent to which foods, inhalants, contactants, and endogenous allergens (metabolic products, faulty intestinal flora, bacteria from focal infection) are responsible in a given case, and the means by which the nature of the causal agent can best be determined.

Although there is a definite tendency at present to minimize the significance of foods in the causation of infantile dermatitis (according to Osborne et al.[882] nutritive allergens account for only 10 to 15 per cent of cases), numerous instances have been reported in which elimination and trial tests conclusively demonstrated that a food—most commonly wheat, milk, egg, orange, tomato, spinach, peas, or cod liver oil—was the sole cause of the condition (Schloss; Blackfan; Ramirez; O'Keefe and Rackemann; Woringer and others). Hill and Pratt[883] stress the fact that milk is to be regarded as two foods, rather than one: the hypersensitiveness may be related to the lactalbumin or to the casein. Occasionally, the physician will have to pay attention to the foods eaten by the mother and possibly reaching the child by way of the breast milk (O'Keefe and Scott; Shannon; Balyeat). Consideration must also be given to the fact that unaltered, undigested protein, such as wheat, alfalfa, flaxseed, and peanuts, sometimes passes intact into cow's milk (Sterling and Fishman,[884]

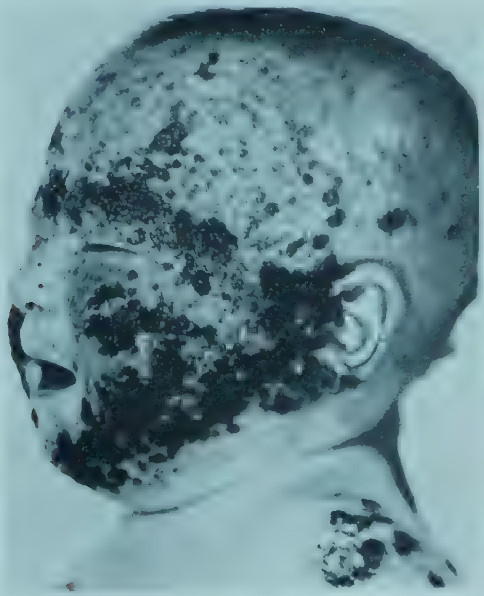


FIG. 138. INFANTILE DERMATITIS. SECONDARILY INFECTED FORM

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[882] OSBORNE, E. D., JORDAN, J. W., and HALLETT, J. J.: New York State J. Med. 42: 47, 1942.

[883] HILL, L. W. and PRATT, H. N.: J. Allergy 12: 143, 1941.

[884] STERLING, A. and FISHMAN, A. E.: Arch. Pediat. 55: 172, 1938.

Rockwell[885]). In these cases the clinical symptoms are due, not to sensitivity to milk, but to the unaltered extraneous protein contained in it.

Horesh[630] reported a series of cases of infantile dermatitis, in patients 7 to 20 months old, in which exacerbations were provoked by odors or vapors from food such as raw egg, fried fish, fried pork, fried bacon, cooked cabbage, or by the presence of dressed fowl. The fact that food may act as an inhalant is usually overlooked. To keep children with dermatitis out of the kitchen when foods are being prepared is therefore sound advice.

Most of the authorities who hold that hypersensitiveness to foods is the cause of infantile dermatitis consider only food proteins. However, there are a few who implicate animal fat. Gartje,[886] for one, blames milk fat as well as cod liver oil and claims, furthermore, that these fat-hypersensitive dermatitic children usually manifest not the exudative but the dry condition so characteristic of seborrheic dermatitis. Because of this assumed allergy to fat, Monrad, Marfan, Gerstley, and others recommended giving children skimmed milk.

If there is a favorable response within a reasonable period of time, the tolerance to fat can be determined by the gradual addition of cream until symptoms recur.

In the case of a nursing infant it is sometimes possible, as claimed by Marfan and Turquety, to reduce the fat content of the mother's milk by placing her on an appropriate diet (limited quantities of fat and meat, no alcohol), thus bringing the milk within the infant's limit of tolerance.

Hypersensitiveness to cod liver oil is sometimes the cause of infantile dermatitis (Balyeat and Bowen,[887] Hoffman and Rattner[888]). It may be pertinent to recall that vitamin A and D preparations are often derived from cod liver oil. The writer observed a severe exacerbation of the skin lesions in a nursling allergic to oleum percomorphum thirty-six hours after the mother ate fish.

Leiner as well as Pulay[889] observed cases of infantile dermatitis in which hypersensitiveness to sugar could be demonstrated. As to the identification of the causative nutritive allergen, Hill and Sulzberger,[890] Osborne and Walker,[891] Finkelstein,[259] Birt,[892] and the writer[26] have long been of the opinion that positive skin tests with food proteins, as well as the passive transfer test and the complement fixation reaction, are undependable and often actually misleading, and that only the elimination diet and,

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885. Rockwell, G. E.: J. Allergy **13:** 404, 1942.
886. Gartje, E.: Monatschr. f. Kinderh. **26:** 57, 1923.
887. Balyeat, R. M. and Bowen, R.: Am. J. Dis. Child. **47:** 529, 1934.
888. Hoffman, S. J. and Ratttner, H.: J. A. M. A. **107:** 494, 1936.
889. Pulay, E.: Deutsche med. Wchnschr. **50:** 1610, 1924.
890. Hill, L. W. and Sulzberger, M. B.: Arch. Dermat. & Syph. **32:** 451, 1935.
891. Osborne, E. D. and Walker, H. L.: Arch. Dermat. & Syph. **38:** 511, 1938.
892. Birt, A. R.: Canad. M. A. J. **43:** 520, 1940.

as we have shown, the Propeptan method are useful and reliable for this purpose.

Although it is true that the majority of all children suffering from infantile dermatitis give a positive reaction to raw egg white, strict elimination of eggs from the diet rarely results in an improvement of the cutaneous condition (Schmidt[893]). Moreover, the skins of these children also react to other kinds of eggs not commonly used for human consumption (pigeon, ostrich, gull, or lapwing). Positive tests with egg white or other foods do not, therefore, permit the conclusion that a given case of infantile dermatitis is necessarily caused by these substances. Such reactions may indicate nothing more than that the skin has acquired a hypersensitiveness to these proteins either during the first weeks or months of life, or perhaps prenatally. This allergic state can pave the way for other hypersensitivities, mediated by ingestants, inhalants, or contactants. Our concept of a metallergic mechanism in infantile dermatitis would seem to be supported by the following clinical observations. After an infectious disease or an exacerbation of one (e.g., tonsillitis, otitis, bronchitis), and occasionally following vaccination or gastrointestinal disturbances, there is a flare-up at the sites of former manifestations, and surprising therapeutic results are achieved by eradication of the foci of infection. Furthermore, the elimination of a great variety of nonspecific external irritants (water, heat, sunlight, friction) often has a decidedly beneficial effect. Hill and Sulzberger[890] venture the opinion that the mechanism in infantile dermatitis is heterophil in nature, that is the dermatitis may be due, for example, not to egg but to allergens immunologically related to egg.

On the other hand, intracutaneous or subcutaneous administration of egg white, milk or flour occasionally brings on severe anaphylaxis, without causing a flare-up of the cutaneous manifestations. In instances of this kind the hypersensitiveness to egg as demonstrated by the skin test, while specific, is not the underlying cause of the dermatitis. Moreover, the feeding of a new protein to an infant (for example, soy bean protein) is followed for a short time by the development of antibodies, as revealed by a positive intracutaneous test (Hill[894]). Elimination or addition of these proteins to the diet will neither improve nor aggravate the condition. Hill therefore interprets the reaction to soy bean as an expression of a nonetiologic, naturally produced hypersensitiveness.

Finally, it should be pointed out that the cutaneous reaction to egg white is of no value as a means of clinical differentiation of the various forms of dermatitis in children. While in the exudative type there is a positive test in the great majority of instances (85 per cent of cases, Sulzberger and

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893. SCHMIDT, F. R.: Illinois M. J. **68**: 376, 1935.
894. HILL, L. W.: J. Allergy **13**: 366, 1942.

Hill; 82 per cent, Moro; 69.5 percent, Strobel and Wasitzky; 65 per cent, Urbach; 54 per cent, Woringer; 50 per cent, Rosenbaum), patients with seborrheic dermatitis not infrequently react in the same manner (Urbach, Miyasaki, Minami). Indeed, some children with the latter condition react with very severe anaphylactic symptoms to injections of egg. For this reason, it is advisable, whenever there is any hint of such danger in the patient's history, never to perform a direct cutaneous skin test on the child, but to employ the passive transfer test of Prausnitz-Küstner. Moreover, intradermal skin tests should, in principle, never be performed unless the child is hospitalized. The present writer has had occasion to observe several instances of late reactions that endangered the young patient's life.

Numerous authors, including Osborne and his associates,[895] Hill,[896] Sulzberger,[852] and Peck and Salomon,[897] are of the opinion that inhalants (e.g., silk, goose feathers, kapok, dust) play the leading role in the causation of infantile dermatitis. For a detailed consideration of this question, the reader is referred to the section above on neurodermatitis.

Contactants may be the causal agents in some few cases of infantile dermatitis. Thus, Tihara,[898] pointing to the strikingly high number of positive reactions to egg white in Japan, attributes this to the popular custom of washing the newborn infant with the white of chicken eggs. As a proof of this theory of percutaneous sensitization, he reports that positive reactions to tests with egg white were obtained in 57 per cent of dermatitic infants who had been subjected to this traditional washing with egg white immediately after birth, while only 16 per cent of those not washed in this manner gave a positive test. Peck and Salomon[897] and Albert and Walzer[899] obtained positive patch tests with silk, goose feathers, and other contactants in patients with infantile dermatitis. Osborne and Walker[891] are also of the opinion that surface exposures are of particular importance in the pathogenesis of infantile dermatitis. They stress the fact, however, that routine patch tests are inadequate and should be replaced by actual clinical trials with woolen capes, gloves, and similar articles of clothing. Furthermore, moisture, friction, and above all, the minute abrasions of the skin resulting from them are necessary to promote epidermal sensitization. Contactants particularly to be suspected are wool, feathers, silk, and other epidermals; kapok; soap and chemicals, including those adhering to underwear and bedclothes after laundering; medicated oils, ointments, medications, and lotions (especially

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895. Osborne, E. D., Jordan, J. W., and Campbell, P. C. Jr.: Arch. Dermat. & Syph. **44:** 604, 1941.
896. Hill, L. W.: J. Allergy **9:** 37, 1937.
897. Peck, S. M. and Salomon, G.: Am. J. Dis. Child. **46:** 1308, 1933.
898. Tihara, R.: Hihu-to-Hitunyo **6:** 302, 1938.
899. Albert, M. and Walzer, M.: J. Invest. Dermat. **3:** 119, 1940.

those containing mercury); insect sprays and floor wax; the mother's cosmetics, including orris root and hand creams and the father's shaving and hair lotions; toys, dyes, and lacquered objects. Finally, the hair and dander of house pets may act as contactants.

Diagnosis

As already mentioned, the differentiation between seborrheic dermatitis and infantile dermatitis is often very difficult to establish. However, in patients of this age seborrheic dermatitis is likely to begin with intertrigo in the groins, axillae, and other folds. Furthermore, blepharitis is very commonly present. Another characteristic symptom is the greasy scaling of the scalp ("cradle cap") (Fig. 152, p. 400), which may extend to other parts of the body, usually to the face, neck, shoulders, and trunk, forming large areas of irregular configuration by fusion. The eruption is essentially a dry, scaly one, usually with rather sharply defined margins, and of a yellowish pink color. The patches do not ooze unless they are rubbed. In severe cases, erythroderma may develop, its severest expression being Leiner's disease (erythroderma desquamativum). The characteristic primary lesion is a red, scaly papule which later is transformed into a greasy, scaly crust.

There is no evidence to indicate that seborrheic dermatitis is of allergic origin. However, seborrheic manifestations so frequently precede the development of infantile dermatitis and mixed forms are so common that there is evidently some relationship between the two (Hill[900]). Finally, the present writer has observed a number of cases of seborrheic dermatitis gradually changing into neurodermatitis.

Infantile dermatitis, on the other hand, is characterized by intense itching, exudation, crust formation, and secondary infection; furthermore, the skin folds are not involved, and there is no blepharitis.

As to the methods of determining the causative allergen, the reader is referred to the section on pathogenesis, where the pitfalls of skin testing and the merits of elimination and environmental tests are fully discussed. The illuminating results of the investigations by Wilmer and his associates, among others, merit special mention. Of forty-four infants who repeatedly had positive reactions to milk and/or egg, definitely allergic symptoms were evidenced by only twelve. Furthermore, the advice of Hill may be appended here, to the effect that if skin testing is undertaken, it should be done by the scratch and not by the intracutaneous method, since even normal infants may give a positive intracutaneous reaction for a short period after eating a food for the first time.

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900. Hill, L. W.: J. A. M. A. **111**: 2113, 1938.

Therapy

Etiologic therapy is the ideal treatment for infantile dermatitis. Unfortunately, however, this approach is very often out of the question, at least at the beginning. It is advisable, therefore, to try a therapeutic program composed of any of the following measures that may seem to fit the individual case: (1) elimination of possible contact or inhalant allergens; (2) correction of demonstrable quantitative or qualitative defects in the diet, and eradication of any existing digestive disturbances; (3) treatment of demonstrable food allergies; and (4) external local therapy, in addition to all forms of etiologic treatment.

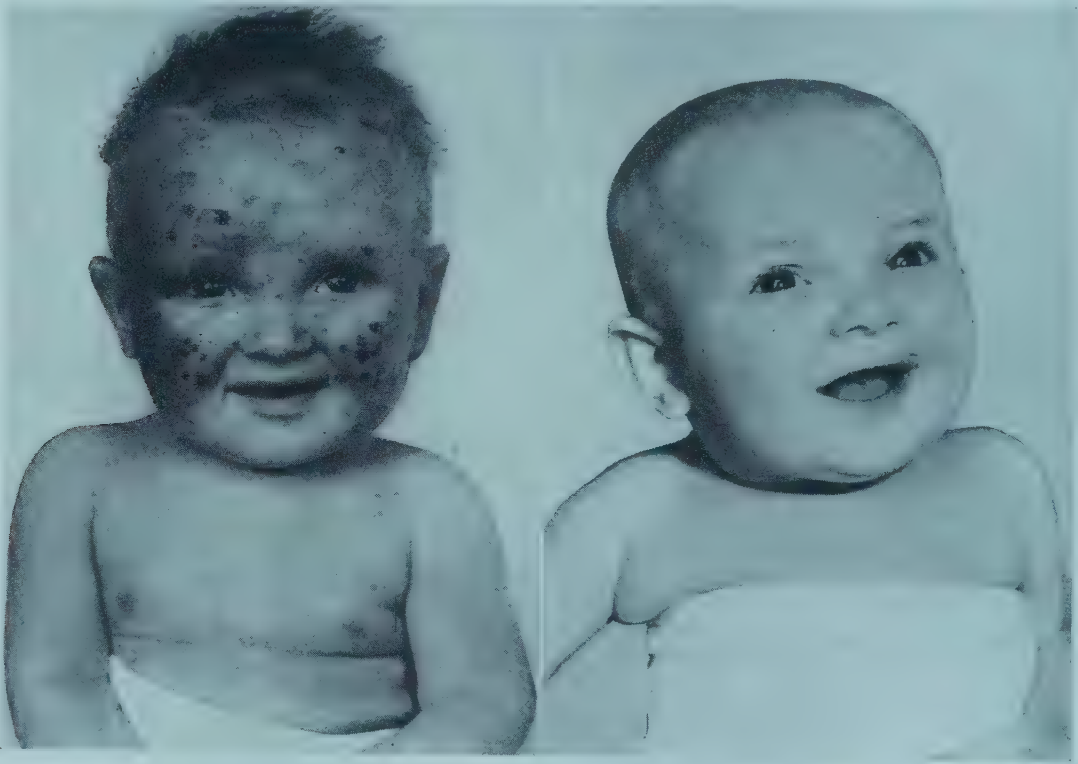

Fig. 139 Fig. 140

Effect of Elimination Diet on Infantile Dermatitis Due to Animal Proteins

Fig. 139. Appearance before treatment.

Fig. 140. After fourteen days of a diet totally free of animal protein.

The first step in management is the elimination of all sources of local irritation and of all known factors of contact allergy. Since many of the agents act as inhalants rather than as contactants, removal of them will also be of benefit in the large group of cases of infantile dermatitis due to inhalant allergy. It is absolutely essential to convince mothers and nurses that their full co-operation is a paramount factor in obtaining satisfactory results.

The child should be placed in a dustproofed room, and should be kept away from (a) such environmental allergens as wool (in clothing and blankets), silk, feathers (in pillows, quilts), and other animal epidermal substances, including dander of pets, as well as house dust and rugs, and (b) chemical substances, including floor wax, insect sprays, medications, cosmetics of the parents, and lacquered toys. It is best to use well washed, unstarched linen or cotton garments. Mattresses, pillows, and blankets should be enclosed in allergen-proof covers. Great care must be taken to ascertain that no soap or laundry chemicals remain in the clothing or bed linen. Thorough and repeated rinsing of all garments and linens is essential. Quite frequently the success or failure of these measures hinges on a personal examination of the child's environment by the physician. Information given by the mother or nurse cannot be entirely depended upon.

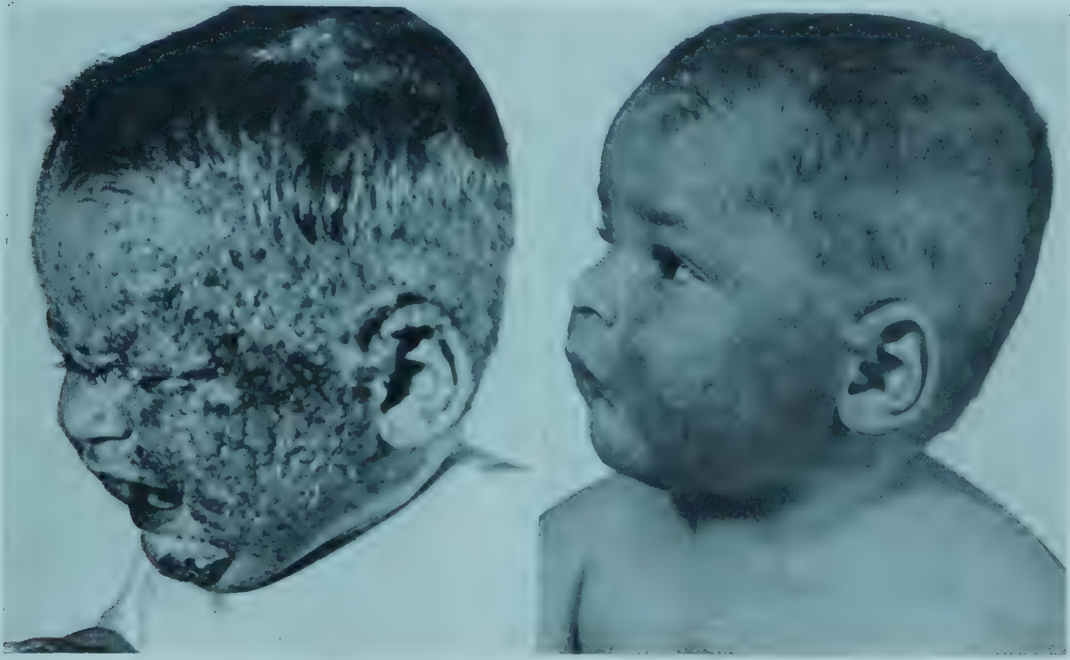
Fig. 141 Fig. 142

Effect of Elimination Diet on Infantile Dermatitis Due to Animal and Vegetable Fats

Fig. 141. Appearance before treatment.

Fig. 142. After twelve days of a fat-free diet.

If this regimen, combined with local treatment, does not bring about improvement within two weeks, elimination diets should be instituted (Figs. 139, 140, 141, 142). These are not only indispensable in treatment, but they constitute a therapeutic test which, for the reasons given above, is superior to skin testing. They can be of value only if strictly adhered to. Elimination diets for the nursing mother frequently produce favorable results in the dermatitic nursling. Needless to say, it is not easy to discover the identity of the allergenic food in the mother's diet. It is said that it is often one for which she had a craving during pregnancy. In the case of milk-fed babies, a first trial with evaporated or superheated milk (kept at a temperature of 240 F. for one half to one hour) may be made, since it has been shown that heated milk has reduced anaphylactogenic properties. However, if this fails, the substitution of goat's milk is sometimes successful (Figs. 143, 144). It is advisable to feed each different form of milk for from five to seven days, since it often requires at least that length of time for any appreciable clinical change to become evident.

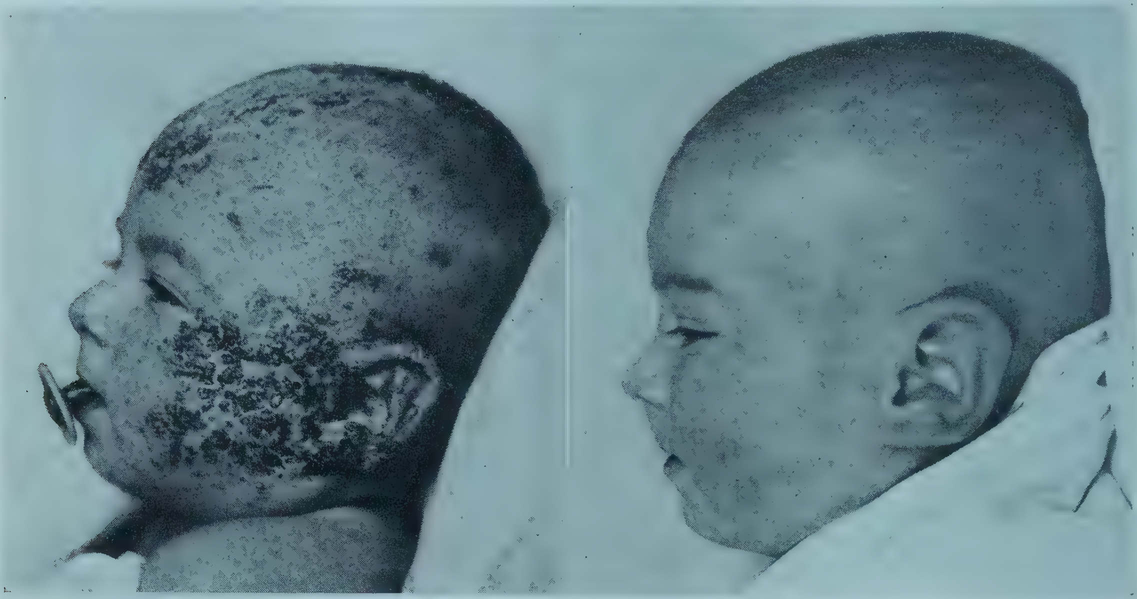

FIG. 143 FIG. 144

EFFECT OF SOY BEAN DIET ON INFANTILE DERMATITIS DUE TO MILK AND MILK PRODUCTS

FIG. 143. Appearance before treatment.

FIG. 144. After twenty-one days on a soy bean diet.

If no animal milk can be tolerated, milk substitutes derived from cereals or vegetables can be used. These are discussed in some detail on page 274. In addition, Glaser[901] and Stuart[700a] advocate the use of strained meats as the protein basis for milk substitutes in the treatment of milk-allergic infants. Liver appears to be of even greater value. It is steamed in its own juices and strained through a fine sieve. From 30 to 50 Gm. of this broth is given two or three times weekly; zwieback serves as a source of carbohydrate.

Since the milk substitutes are poor in vitamin potency, synthetic preparations should be given. Synthetic vitamin A (carotene, 8 to 10 drops daily), vitamin B (the contents of 2 capsules of B complex each day, given in the feedings), vitamin C (ascorbic acid, 50 mg. daily), and vitamin D (Drisdol, 8 to 10 drops daily) must be added to supplement the food. Synthetic vitamins are preferable in order to avoid occurrence of an allergy to any protein contained in the natural vitamin sources (cod liver oil, yeast, liver).

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[901] GLASER, J.: J. Allergy 15: 283, 1944.

The effects of the diet should become apparent within a week. After the condition has healed or materially improved, the following foods may be added one at a time, at three day intervals, according to the infant's age, desire, and digestive and allergic tolerance: corn meal, rice, oatmeal, wheat flour, tapioca, carrots, lettuce, asparagus, bananas, and bread.

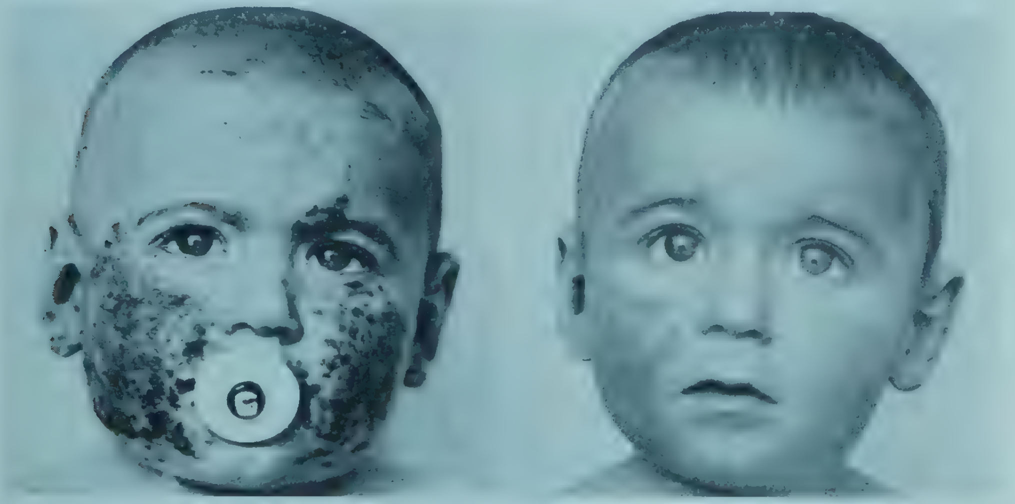

FIG. 145 FIG. 146

EFFECT OF PROPEPTAN THERAPY IN A CASE OF INFANTILE DERMATITIS DUE TO COW'S MILK

FIG. 145. Appearance before treatment.

FIG. 146. After four weeks of administration of cow's Milk Propeptan.

Reactions should be carefully noted. If the condition flares up after a certain food has been added to the diet, this item should be withheld until the eruption has disappeared. Milk, eggs, tomatoes, and oranges are the last foods to be tried.

For the purpose of observing the effect of this regimen a "food diary" is of particular help. It consists of a complete, carefully kept record, with notations of the time of ingestion of each food, including such ordinarily overlooked items as sweets, on the left-hand page, and of fluctuations in the symptomatology in some detail on the right-hand page.

Another method of management of food allergy causing infantile dermatitis is Propeptan therapy. This approach is discussed in some detail on page 267. Figures 145 and 146 show an exudative type of infantile

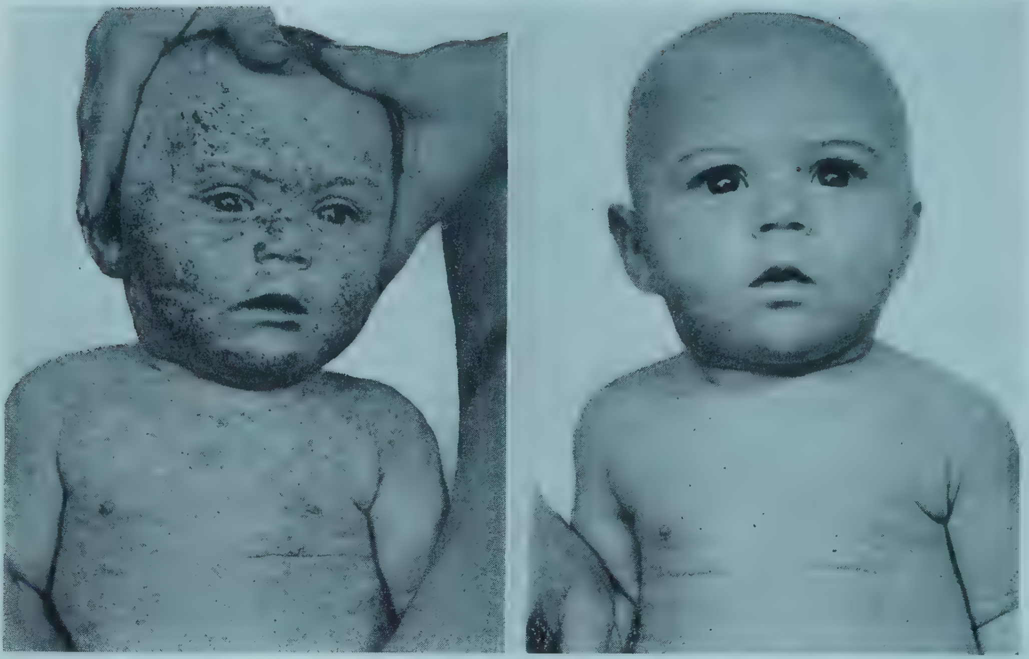

Fig. 147 Fig. 148

Effect of Propeptan Therapy in a Case of Infantile Dermatitis Due to Cow's Milk and Milk Products

Fig. 147. Appearance before treatment.

Fig. 148. After twenty-one days of administration of Milk Propeptan.

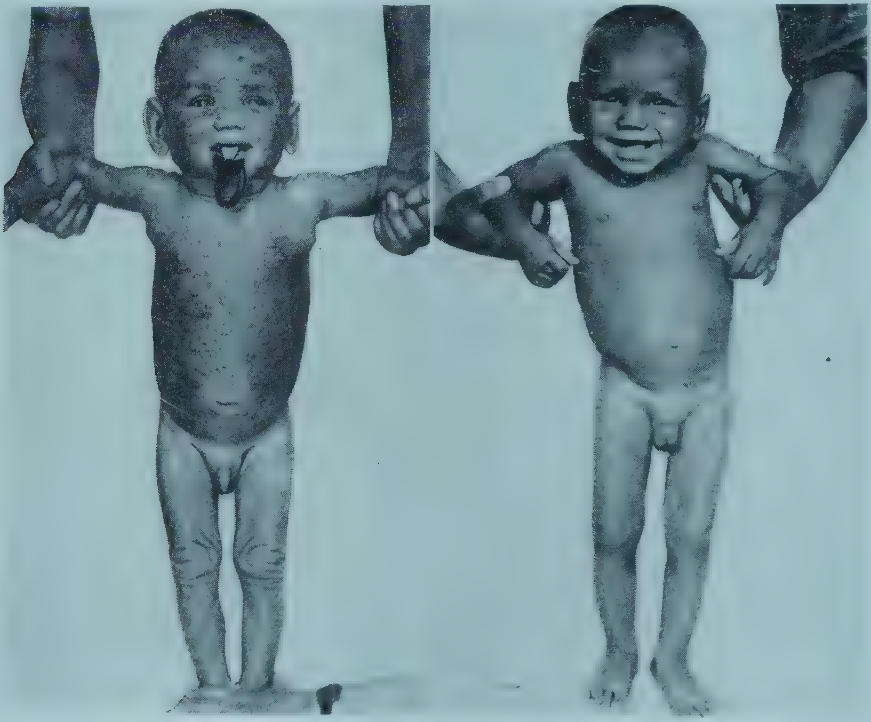

Fig. 149 Fig. 150

Effect of Propeptan Therapy in a Case of Severe Neurodermatitis Due to Wheat Allergy

Fig. 149. Greatly undernourished infant with characteristic neurodermatitic lesions.

Fig. 150. Four weeks after systematic administration of Wheat Propeptan.

dermatitis, confined to the face, due to milk hypersensitiveness. Figures 147 and 148 present the chronic form. Figures 149 and 150 show the generalized distribution which later on leads to neurodermatitis; this case, due to wheat allergy, was entirely controlled by Wheat Propeptan.

Undernutrition, diarrhea and infection, if present, must all be cleared up in the exudative as well as in the seborrheic type of dermatitis in children. The writer has quite frequently observed the onset of skin manifestations in infants after prolonged diarrhea. It seems likely that the intestinal allergization was initiated by the diarrhea. Furthermore, the author has repeatedly seen that focal infections, such as tonsillitis, otitis, bronchitis, and pyelitis, as well as those in the intestines, may produce rather severe exacerbations of the skin disease.

Dietary Therapy

From the standpoint of nutritional therapy, we subdivide children with infantile dermatitis into four groups: (1) overfed infants; (2) atrophic and dystrophic infants; (3) children with exudative diathesis; and (4) children who must be regarded as eutrophic, clinically, but who nevertheless exhibit refractory cutaneous manifestations.

The first mentioned and numerically quite important group comprises the fat children with dermatitic symptoms. In a given case it is important to determine whether the child is an overfed infant or of the exudative type, not only for the purpose of prescribing the proper dietary therapy, but also to be in a position to estimate the probable duration of the disease. Fig. 134 on p. 377 shows an overfed infant; the turgor of its skin is much firmer than in the typical exudative child; furthermore, its legs are also quite fat, while the legs of the exudative infant are relatively thin (Fig. 133 on p. 377).

When dealing with an overfed nursing infant, the intake must be regulated in such a manner that the weight curve rises slowly. The child is not to nurse more than four times a day, and the quantity of milk consumed should be less than that allowed normal children (i.e., some 750 Gm. after the third month). Should this quantity prove insufficient, milk may be replaced once or twice a day by foods prepared from cereals. Bottle-fed infants are to be dealt with similarly: they are to receive no more than 75 per cent of the usual quantities of milk, carbohydrates, and fats; in some instances it may be well to replace one of the regular meals with unsalted, moderately sweetened gruel. In older infants it is advisable to omit permanently some of the milk earlier than is usual and to begin giving salt-poor vegetables and gruels cooked in water. In these cases some of the missing protein may be supplied by small quantities of casein. Weeping dermatitides often yield to dietary therapy of this kind, supported by appropriate local treatment.

Children belonging to the second group, the atrophic and dystrophic infants, are to be given an entirely different form of dietary therapy. In the first place, they must be divided into two categories: (1) those who have developed poorly since birth because of some constitutional peculiarity, as, for example, breast-fed babies who fail to thrive and who are termed "atrophic"; (2) those who develop satisfactorily at first but then, because of some alimentary or infectious complication, lose strength and are in a state of undernourishment for some time, so-called "dystrophic" children. When dealing with both the atrophic and dystrophic infants (Fig. 135 on p. 377), who present a picture generally dominated by dry, disseminated dermatitic skin manifestations, dietary therapy is to be instituted in accordance with the pediatric principles for the treatment of the various degrees of atrophy. Digestive symptoms are to be treated with the indicated dietary measures (buttermilk or protein milk) or, if necessary, the child should be returned to breast feeding. If intestinal disturbances are present a detailed history should be obtained in order to determine whether the condition is due to undernourishment or to an unbalanced diet (preponderance of milk, excessive intake of gruel, bread, etc.), and the discovered fault in the diet is then to be corrected.

Lederer[902] stresses the fact that nursing infants who do not thrive and who have frequent bowel movements not uncommonly present dry and scaly dermatitides or weeping dermatitic lesions localized almost exclusively in the genital and gluteal zones; and that, as nutritional experiments have shown, this condition is attributable to relative quantitative or qualitative protein inanition. He distinguishes two groups. The first is characterized by frequent vomiting and numerous bowel movements, which often occur while the child is nursing and during which the stool is evacuated not in great quantities, but rather in the form of "splashes," usually very loose, watery, greenish, and sometimes containing mucus. Since such enteritis is often attributed to overfeeding, these children are mistakenly put on a starvation diet, given tea, laxatives, and similar measures, as a result of which the symptoms grow worse. Actually, however, this condition is not a true diarrhea at all, but the expression of a constitutional defect (heightened irritability of the intestinal nervous mechanism peculiar to these infants), which can be overcome by feeding the child generously. When the general inanition has been corrected, the cutaneous manifestations often regress with amazing promptness. Should the mother be unable to supply the child with enough milk, one must resort to supplementary feeding.

Then there is a second group, composed of infants who fail to thrive despite adequate nursing, and who exhibit dermatitis. In these cases, according to Lederer, the physician must make certain that the infant receives adequate amounts of protein. The test is made with a mixture from 5 to a maximum of 10 Gm. of calcium caseinate in a minimal quantity of cow's milk (stirred when cold, then boiled for five minutes and sweetened somewhat with saccharin). If treatment with this preparation discloses the presence of protein deficiency, the child may be put on a diet consisting in part of cow's milk (one or two meals daily). In these cases the milk may be given in a slightly more concentrated form than usual (approximately ⅔ milk up to the age of 3 months). The infants frequently thrive splendidly on the supplementary protein and the dermatitis often disappears. Should the increase in protein fail to achieve results, the addition of some flour (3 per cent) may be warranted, provided the infant is at least 6 weeks old. In many cases of this kind, the constitutional deficiency seems to involve not only protein, but carbohydrates as well; in that event, administration of supplementary quantities of the latter will correct this defect. The physician must see to it that the child receives sufficient vitamins, particularly vitamin B complex (Harris and Gay,[903] Epstein[856]).

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[902] LEDERER, K.: Die Ernährung der Sauglings an der Brust. Berlin: Springer, 1926.

Special attention must be given to the diarrheal diseases, particularly to the entire question of regulating the intestinal function, since disorders of this kind sometimes constitute the predisposing cause of food-allergic dermatitis developing later in life. With regard to the treatment of the diarrheal diseases in infancy, we must refer the reader to the special textbooks on infant care.

We should like to state at this juncture that infants who do not thrive on the breast or who become dystrophic do not necessarily have to be weaned. On the contrary, in cases of this kind it is best to give supplementary amounts of diluted cow's milk or of buttermilk which must, however, be prepared with flour alone (i.e., without sugar) for children suffering from diarrhea. Furthermore, it is advisable to modify the mother's diet in such a manner that her milk will contain less fat. When these children attain normal weight, their cutaneous symptoms generally disappear quite rapidly.

We shall now consider the third group, that of infants exhibiting symptoms of Czerny's[904] "exudative diathesis." In addition to the flabby constitution, this diathesis is characterized by cutaneous manifestations which include the so-called "milk crust" which affects the face, especially the cheeks and forehead, while sparing the mouth. This condition first takes the form of an erythema covered with thin, friable scales (Fig. 136 on p. 378) and then, as it progresses, presents intensely pruritic, generally excoriated, and crusted groups of vesicles on an infiltrated, acutely hyperemic base (Fig. 137). The exudative foci naturally constitute an excellent medium for the growth of bacteria, which explains the frequent occurrence of secondary infectious dermatitides, principally on the face (Fig. 138), and of swellings of the regional lymph nodes. These children are further characterized by pallor and a bloated appearance.

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[903] Harris, A. and Gay, L. N.: J. Allergy **14:** 182, 1943.

[904] Czerny, A.: Des Kindes; Ernährung, Ernährungsstörung und Ernährungstherapie. Leipzig: Deuticke 1930.

The objective of dietary therapy in these infants is to convert the constitutionally abnormal (hydrolabile) condition of the organism to normal.

A restricted diet low in fat and salt, as suggested by Czerny[904] and elaborated by Finkelstein,[259] induces an appreciable weight reduction in obese children, exerts a beneficial influence on the tissues generally, and thus frequently leads to a marked improvement of the dermatitic manifestations. Breast-fed infants are to be allowed no more than 4 or 5 feedings a day. Should such restriction prove inadequately effective, one or two feedings may be replaced by malt soup or by a 5 per cent porridge of flour. In bottle-fed children, the principal change in the diet is the reduction of the intake of milk to ½ or even ¼ liter daily and substitution of barley gruel, or porridge of flour or semolina. The danger of rickets can be obviated by administering 10 drops of viosterol daily. Quite early (when the child is 3 or 4 months old) one can go over to a diet of vegetables, scraped fruit, and unsweetened stewed fruit. Meat broths are to be avoided. If this dietary does not bring marked improvement in three or four weeks, milk may be excluded entirely for two to four weeks, giving a diet composed of tea, flour porridge, gruel, fruit, and vegetables, and meeting the protein requirements with finely sliced white cheese, calcium caseinates or protein hydrolysates. The writer has obtained gratifying results with the "eczema soup"* of Finkelstein[259] in children over 6 months of age, when it was used strictly in accordance with his instructions. It should be employed only in weeping dermatitides in infants who have well formed stools and who are not suffering from any debilitating infection.

* Finkelstein's "eczema soup" is prepared in the following manner: To 1 liter of raw whole milk (34°C.) add 1 rennet tablet, and allow the mixture to stand in a water bath at 50°C. for thirty minutes to an hour, until the curd forms. Then the mixture is strained through a cloth so that the casein is separated from the whey (this procedure takes another half hour). The curd, with a little water added, is then gently forced through a fine sieve six or seven times, after which it is brought to a boil while being vigorously stirred. One hundred to 200 Gm. of whey is added, and then water or gruel (2 to 3 per cent) to bring the volume up to 1,000 cc. Lastly, 50 Gm. of carbohydrate (but no dextrin or malt sugar) is added. The soup has been properly prepared only if the casein is in the form of minute particles. In addition, the infant is given porridge, vegetables, and stewed fruit, as is customary in its ordinary diet.

Although the purpose of this regimen is to prevent a further excess weight gain, care must be taken to avoid too rapid weight loss, except in the very first days of treatment. The infant's health in general must not be jeopardized, merely for the sake of achieving some possible external improvement. Whenever the loss in weight seems excessive, the intake should be increased by giving the supplementary items as already mentioned (gruel, vegetables, stewed fruit) and sometimes even by increasing the quantity of whey in the "eczema soup," and adding salts to the vegetables, so that the body may develop normally. The soup is to be given for some two to four weeks until the weeping ceases, after which the child is placed on a diet containing relatively small amounts of milk.

Schiff prescribed the following diet for exudative children suffering from dermatitis. First meal: 150 to 200 Gm. of almond milk* (without whey), with 8 per cent sugar and 1 teaspoonful of almond flour or zwieback added. Second meal: 3 ripe mashed bananas are thoroughly mixed with 1 teaspoonful of sugar; 4 to 6 teaspoonfuls of raspberry juice may be added. Thirty cc. of fruit juice is also given at this feeding. Third meal: 150 Gm. of vegetables are cooked in water without salt for fifteen minutes, puréed very fine, and then mixed with 30 or 50 Gm. of mashed potato. In addition, the infant is fed 30 cc. of fruit juice. Fourth meal: same as the first. When the dermatitis begins to show marked improvement, the child may be given a more substantial banana mash.†

The youngest child placed on this regimen by Schiff was 4 months old. It was found that the diet almost invariably brought about a weight reduction of 100 to 150 Gm., which apparently had no effect on the patient's general condition. The almond milk was never continued for more than two weeks, being gradually replaced by buttermilk or whole milk given in the same amounts. According to Schiff, the efficacy of this therapy was seen in prompt regression of the severe, extensive dermatitis and in alleviation of the very intense itching within a few days.

Di Sant' Agnese and Larkin[906] found impairment of vitamin A absorption in intractable infantile dermatitis. These authors, as well as Redaelli,[261] noted improvement following therapeutic doses of this vitamin.

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* Fifteen Gm. of almonds are allowed to soak in 100 cc. of water for twelve hours, after which they are shelled. The almonds are then puréed and thoroughly mixed with the water for thirty minutes. Lastly, the mixture is strained through a cloth and briefly brought to a boil.

† Two or 3 zwieback biscuits are soaked in 150 cc. of water, 10 Gm. of sugar is added and the mixture is brought to a boil, stirring constantly. The zwieback mash is then enriched with one or two mashed bananas. When the dermatitis has disappeared almost completely, the gruel may be further increased calorically by the addition of 5 Gm. of wheat flour mixed with 5 cc. of salad oil.

906. Di Sant' Agnese, P. A. and Larkin, V. deP.: Soc. Proc. Exper. Biol. & Med. **52:** 343, 1943.

Another approach is the one pioneered by Hansen[907] and based on the observation that a goodly percentage of infantile dermatitis cases are associated with a fat deficiency of a specific character as manifested by a low level of unsaturated fatty acids in the blood serum. Hansen,[908] Faber and Roberts,[237] and others have reported encouraging results obtained by giving the children fats rich in unsaturated fatty acids such as Soyola (3 to 6 teaspoonfuls daily). When the child has reached the age of 6 months, he may be given soups with groats, corn meal, rice, or sago added; and somewhat later a variety of vegetables, stewed or scraped raw fruit without too much sugar. From the age of 9 months on, finely chopped meat may be given twice a week; as soon as dentition begins, bread is allowed. Eggs are strictly prohibited, and cream, butter, and sweet puddings and pastry are also to be avoided. The daily intake of milk should never exceed 200 cc.

A trial may be made with hydrochloric acid milk,* as suggested by Scheer,[910] or with buttermilk, as has been advocated by Fehr. Even in their second year these hydrolabile children should be given as little milk as possible, but an abundance of vegetables is desirable. From the age of 13 months on, their protein requirements should be met with a supplement of finely chopped meat (1 to 2 teaspoonfuls daily). Eggs are definitely contraindicated for children with dermatitis, as late as the second and third year.

In any event, whether or not the above described nutritional therapy proves beneficial, every child belonging to this group should be investigated for any possible food allergy (p. 379), since the latter may pay an etiologic role.

Lastly, there is a fourth group composed of infants with refractory dermatitides, who are neither too fat nor too thin, neither exudative nor atrophic—in short, children whose nutritional state must be regarded as eutrophic. Should the history reveal any dietary errors (undernourishment, overfeeding, unbalanced diet, such as excessive quantities of milk, porridge, bread), these are, of course, to be rectified at once. Similarly, any digestive disturbances must be appropriately dealt with. In children of normal development who become afflicted with dermatitis while on a diet conforming quantitatively and qualitatively with the normal requirements, buttermilk is sometimes very beneficial. In other cases of this kind, improvement may be achieved by changing the diet completely, giving what is known as a "contrast diet" which consists, for example, of interposing malt soups, buttermilk, or flour browned in hot fat between the regular milk mixtures, or by replacing butter with margarine (Langstein[911]). Here it is not unlikely that a radical change in the bacterial flora of the intestine, due to alteration of the latter's contents, may play a significant role. It is also possible that this may in turn influence and alter the pH of the various portions of the intestinal tract. Moreover, this same alterative action (*Umstimmung*) seems to be involved in treatment with hydrochloric milk, as suggested by Scheer, for which reason this method is well worth trying. In occasional instances we have obtained gratifying results with a raw food diet, including the so-called Bircher muesli (mousse).*

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* To 250 cc. of boiled and cooled milk add, stirring constantly, 10 cc. of normal hydrochloric acid drop by drop until a pH of 4.2 is reached. For smaller children a ⅔ milk-⅓ water mixture can be used instead of whole milk. Hydrochloric acid milk prepared in this manner is equivalent in acidity to naturally soured milk. It is diluted by the addition of 3 or 4 parts of boiled and cooled water to 1 part of hydrochloric acid milk, stirring constantly. The mixture is to be heated to body temperature and 6 per cent carbohydrate added before serving. From 200 to 600 cc. is given daily.

907. Hansen, A. E.: Proc. Soc. Exper. Biol. & Med. **30:** 1198, 1933
908. Hansen, A. E.: Proc. Soc. Exper. Biol. & Med. **41:** 205, 1939.
910. Scheer, K.: München. med. Wchnschr. **7:** 852, 1928; Klin. Wchnschr. **9:** 569, 1930.

In closing the discussion of nutritional therapy of infantile dermatitis we would like to second the warning of Buchanan and co-workers[912] against the injudicious use of diets. While withholding protein or fats for a few weeks will not harm the child, prolonged restriction of the caloric, mineral, and vitamin values, as well as of specifically excluded basic food constituents, may be definitely harmful.

Local Therapy

In addition to the general and dietary management, external local treatment is indispensable, though it is in itself merely palliative, not curative. To begin with, bathing is strictly forbidden, and only the uninvolved skin areas may be washed with soap and water. The affected skin may be cleansed with plain petrolatum, mineral oil, olive oil, or preferably by means of compresses. In order to prevent scratching of the lesions and avert the consequent danger of secondary infection, the arms and legs should be restrained by tying them to the sides of the bed. In milder cases, the arms may be splinted with stiff cardboard cuffs covered with cotton and reaching well above the elbows (Fig. 151). The fingernails should be kept closely trimmed.

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* Bircher Muesli (mousse): A level tablespoonful of oatmeal flakes (approximately 10 Gm.) is soaked in 3 tablespoonfuls of water for twelve hours; just before serving, the softened flakes are thoroughly mixed with the juice of half a lemon and 1 tablespoonful of sweetened condensed milk; then 150 Gm. of grated raw apple (including skin) is mixed into the mash. Care must be taken to grate and mix in the apple a little at a time in order to avoid needless exposure of the fruit to the air. The mixture is then sprinkled with ground nuts such as almonds or hazel nuts. Instead of sweetened milk, pure honey may be used; and the latter, with water added, must be warmed in a water bath and thoroughly mixed. Instead of apple, any other fruit in season may be used (finely chopped or grated, of course). Children relish the muesli mixed with strawberries.

911. Langstein, L.: Therap. Monatshefte **32:** 338, 1916.
912. Buchanan, R. N., King, H., and Hamilton, C. M.: J. Tennessee State M. A. **36:** 89, 1943.

If the infant rubs the face on the bedclothes, Stoesser[913] advises the use of a sheet of anti-frost shield material such as is placed on automobile windows during the winter. A piece about two feet square is fastened to the bed beneath the head of the baby by adhesive strips running along the edges. A large x-ray film from which the emulsion has been removed may be similarly employed.

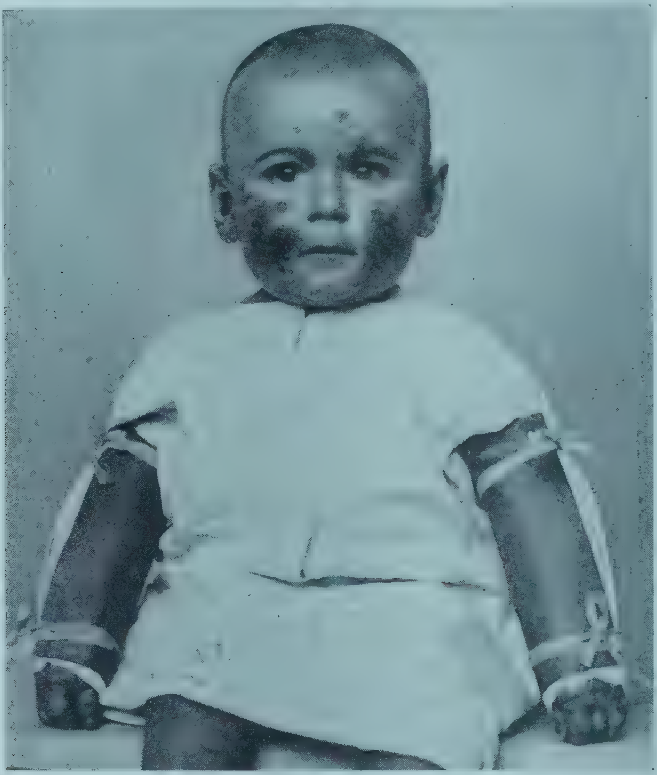

Fig. 151. Method of Restraining Child with Infantile Dermatitis from Scratching

In acute cases the condition can be relieved by wet dressings of 2 per cent boric acid solution, 1:10,000 acriflavine solution, diluted Burow's solution, or potassium permanganate in a 1:5,000 dilution. These are applied to the most severely affected areas three times daily for one hour, being changed every ten minutes. In severe cases it will be necessary to cover the face with a mask of linen coated with a thick layer of boric acid ointment (U.S.P. IX without wax) and to apply the compresses over the mask. In the event of secondary infection, penicillin ointment (500 units penicillin per cc. of aquaphor) may be used instead. When there is no more crusting or infection, the wet dressings may be placed directly on the face and the following lotions may be thinly and gently applied in the intervals between the wet dressings:

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[913] Stoesser, A. V.: Regional Course of American College of Allergists, 1944.

	Gm. or Cc.	
℞ Olive oil	aa 15.0	aa ʒ iv
Zinc oxide		
Talc		
Glycerin		
Water	aa q.s. ad 100.0	aa q.s. ad f℥ iii

	Gm. or Cc.	
℞ Bismuth subgallate	aa 15.0	aa ʒ iv
Zinc oxide		
Talc		
Cottonseed oil		
Glycerin		
Water	aa q.s. ad 120.0	aa q.s. ad f.℥ iv

When the acute dermatitis has subsided, crude coal tar, beginning with 0.25 per cent and slowly increasing to 5 per cent, is extremely valuable if well tolerated. For the first two days the tar ointment should be applied to a limited area in order to determine whether it irritates the skin.

	Gm. or Cc.	
Crude coal tar	0.6–6.0	gr. x—ʒiss
Olive oil	20.0	ʒ v
Zinc paste	q.s. ad 120.0	q.s. ad ℥iv

Naftex (Lascoff)	6.0–30.0	ʒiss—℥i
Zinc paste	q.s. ad 60.0	q.s. ad ℥ ii

In severe cases, small fractional doses of x-rays are sometimes of value.

If sedation is necessary, chloral hydrate and phenobarbital are preferred; bromides should not be used. According to Stoesser,[913] a dose of the medication given only occasionally is not very effective. The infants require fairly large amounts of the sedatives before they become quiet. The average dose of chloral hydrate is 0.06 to 0.12 Gm. (gr. i or ii) and of phenobarbital 0.01 to 0.015 (gr. 1/6 to 1/4) given every four hours.

Dermatitides in Older Children

While the foregoing section was devoted to the various forms of dermatitis in infants and small children to about the end of the second year, we shall now discuss those seen in children 2 years of age and older. We believe that it is necessary to make this distinction for clinical reasons and for the purposes of nutritional therapy. When the children of the overfed as well as the atrophic type reach the age of 2 years, their dermatitic lesions retrogress almost completely. Furthermore, the number of exudative children becomes much smaller at that time of life. At this age, neurodermatitis begins to play a dominant role, not infrequently appearing in children who have exhibited the clinical picture of infantile dermatits during their first two years. While the latter was chiefly exudative, affecting the face and adjacent areas of the neck and chest, neurodermatitis shows a marked predilection for the joints (wrists, elbows, inguinal folds, backs of the knees), and is characterized by dry lesions which show a tendency to lichenification and are accompanied by distressing and intense itching. In dermatitides of this kind, excellent results may often be obtained with the raw fruit and vegetable diet as prescribed by Schiff.[905]

For periods of two and in occasional instances three weeks, the children, all of whom were over 2 years old, were given nothing but uncooked foods such as raw fruit, raw tomatoes, carrots, and the like. When there were definite signs of improvement, the patients received for breakfast about 100 cc. of milk with malt or diluted with tea, and at the mid-day meal small amounts of vegetables, prepared without salt, and a little meat. Two or three small rolls, with unsalted butter, were allowed daily. At the same time, the intake of liquids was restricted to a minimum, and sodium chloride was excluded from the diet for many months. Finally, the children were given a mixed diet high in vegetables and very low in table salt. For several months following complete disappearance of the skin manifestations, a strict fruit diet was observed on occasional days, at first twice and then once a week. A temporary, minor loss in weight was soon regained. That this regimen serves to clear both the disseminated and the circumscribed forms of neurodermatitis in a rather short time has also been the experience of the present writer (Figs. 131, 132 on page 374).

In addition to the chronic dermatitides there are the more acute as well as subacute forms without characteristic localization. In these conditions an underlying food allergy can sometimes be demonstrated by elimination diet (see p. 243) or by means of a Propeptan diet. Fig. 118 on page 358 shows a boy, aged 3 years, whose dermatitis persisted until we discovered, by means of the Propeptan method, that horse meat, in the form of horse meat sausage, was the causal food allergen. The cutaneous symptoms cleared when we removed this item from the patient's diet. Rowe[914] and others have reported similar observations. For further discussion of neurodermatitis, the reader is referred to pages 202 and 366.

[914] Rowe, A. H.: Arch. Dermat. & Syph. **16:** 514, 1927.

F. SEBORRHEIC DERMATITIS

On clinical grounds, Unna segregated from the dermatitis group certain cutaneous manifestations which are commonly encountered in the so-called seborrheic regions and called them "seborrheic eczema." Most dermatologists are now inclined to accept this concept with some reservations (Ormsby and Montgomery[915]). Seborrheic dermatitis, as it is now generally termed, is distinguished from other dermatitides by the morphology of its lesions, i.e., the production of erythematous, scaly patches which, when oozing, constitute diffusely moist areas unlike those produced by a weeping vesicular dermatitis (Gross[840]). Marchionini[116] demonstrated abnormally high cholesterol levels in the upper skin strata in such areas of the body as the axillae, cheeks, and hairy scalp in patients with status seborrheicus. Furthermore, Walter and Obtulowicz[119] showed that the lipid content of the blood serum of patients with seborrheic dermatitis is different from that seen in normal individuals; there is a considerable shift of the cholesterol-lecithin ratio. These authors also found similar changes in the relative quantities of cholesterol esters and lecithin in the epidermis of the lesions of seborrheic dermatitis. Since the symptomatology and therapy of seborrheic dermatitis in infants are quite different from those in older children and adults, we shall discuss them separately.

Seborrheic Dermatitis in Infants

A clinical discription of seborrheic dermatitis in infants was presented on page 383. Differentiation between this condition and infantile dermatitis is often difficult (Urbach[915a]). Moreover, as mentioned elsewhere (p. 383) both types of dermatitis sometimes occur in the same infant, either consecutively or even concurrently. According to Finkelstein,[259] seborrheic dermatitis is a primary disturbance of the protein and fat metabolism in the skin, resulting in dyskeratosis with secondary inflammation. Infantile dermatitis, on the other hand, is a primary exudative inflammation with secondary dyskeratosis.

Seborrheic dermatitis is characterized by the eruption of plaques with more or less fatty scales. Since these plaques resemble those of psoriasis, some authors prefer to term the condition "psoriasoid." They can become confluent and form larger patches. This occurs particularly on the scalp, forming a thick fatty crust, the so-called "cradle cap" (Fig. 152). The cheeks may be unaffected, but, as often as not, a hyperemic, scaly infiltration develops there. The disease shows a definite preference for regions exposed to maceration, notably the genitocrural zone (Fig. 153),

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915. Ormsby, O. S. and Montgomery, H.: Diseases of the Skin. Philadelphia: Lea and Febiger, 1943.

915a. Urbach, E.: Wien. Klin. Wchnschr. 45: 1228, 1932.

and for all areas where cutaneous surfaces are in apposition with one another, such as the cutaneous folds, articular creases, the axillae, the bend in the elbows, the fold of the neck in fat children, and the folds at the beginning of the lobe of the ear. The extent of the areas of intertrigo depends on the severity of the disease. It is important to note that regions where there is a considerable secretion of cutaneous fat, such as the scrotum, the navel, and the margins of the eyelids, are especially susceptible. Blepharitis is a frequent symptom of seborrheic dermatitis. The younger the child, the more pronounced the extensive intertriginous cutaneous changes (Fig. 154); the older the child, the more dominant are the psoriasis-like eruptions (Figs. 155, 156). In young infants, the char-

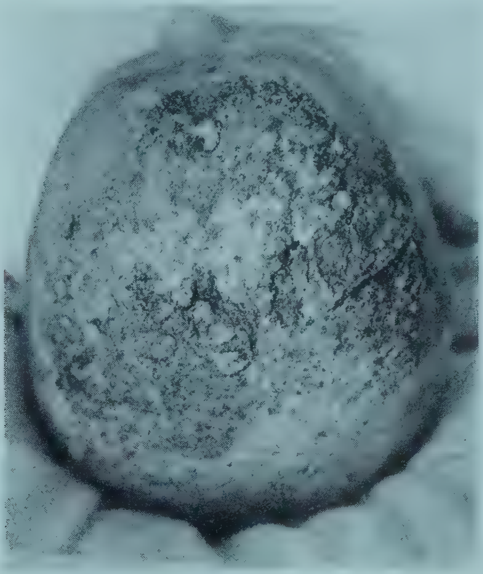

FIG. 152. SEBORRHEIC DERMATITIS LIMITED TO SCALP: "CRADLE CAP"

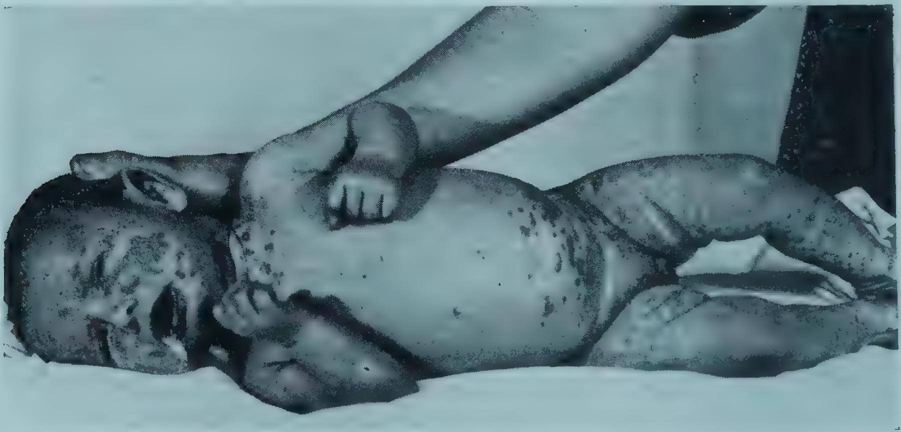

FIG. 153. SEBORRHEIC DERMATITIS INVOLVING FACE, GENITOCRURAL REGION, AND LOWER EXTREMITIES

acteristic type is that which when fully developed is called erythroderma desquamativa, or Leiner's disease; this is distinguished by extensive, often

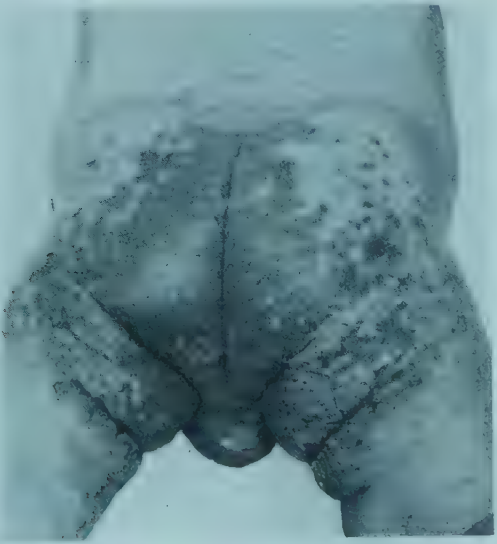

FIG. 154. SEBORRHEIC DERMATITIS IN AN INFANT

Note that the involvement is chiefly confined to intertriginous regions

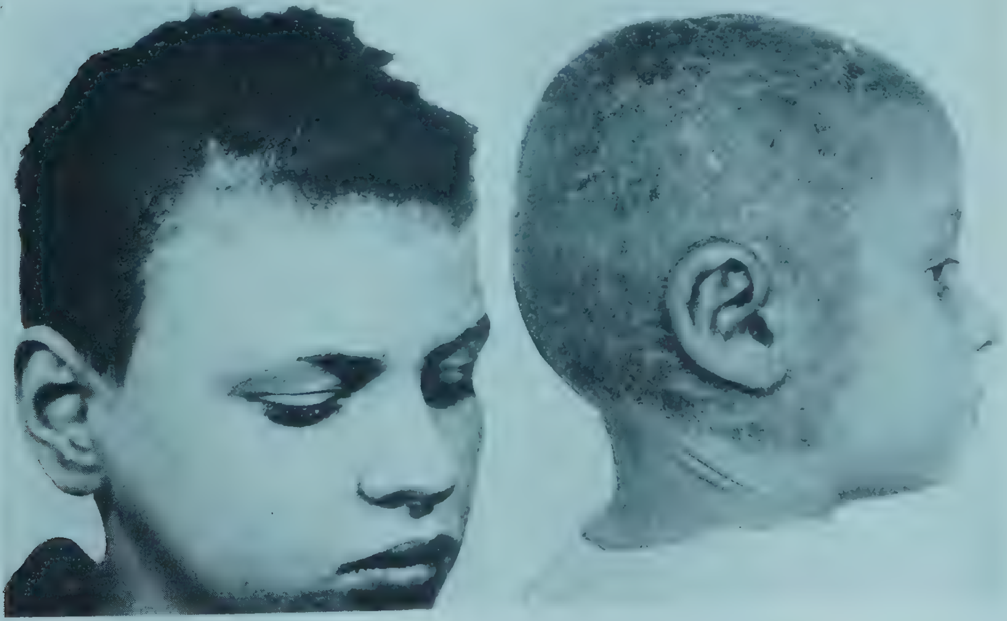

FIG. 155

FIG. 156

FIGS. 155, 156. SEBORRHEIC DERMATITIS IN CHILDREN

Note the resemblance to psoriasis vulgaris

universal scaliness and redness of the skin, resembling general intertrigo (Fig. 157).

In breast-fed infants with a predominantly seborrheic type of dermatitis, one may try to decrease the fat content of the mother's milk by placing her on a low milk and low fat diet. Should this device fail, partial replacement of the mother's milk by low fat formulas is indicated. In many cases satisfactory results can be obtained by substituting for one or two breast feedings corresponding amounts of buttermilk plus an adequate supplement of carbohydrate (6 to 8 per cent). Finkelstein[259] advocates giving 10 to 15 Gm. of protein powder (calcium caseinate or a similar preparation) in tea or in mother's milk obtained by pumping the breast. Finely chopped liver (15 to 30 Gm. daily), sometimes in the form of a liver and zwieback mash, has proved helpful. It is noteworthy that infants with seborrheic dermatitis often have thin, greenish stools when on a diet of mother's milk alone and that they often become normal when supplementary protein is given. However, complete weaning is not generally approved.

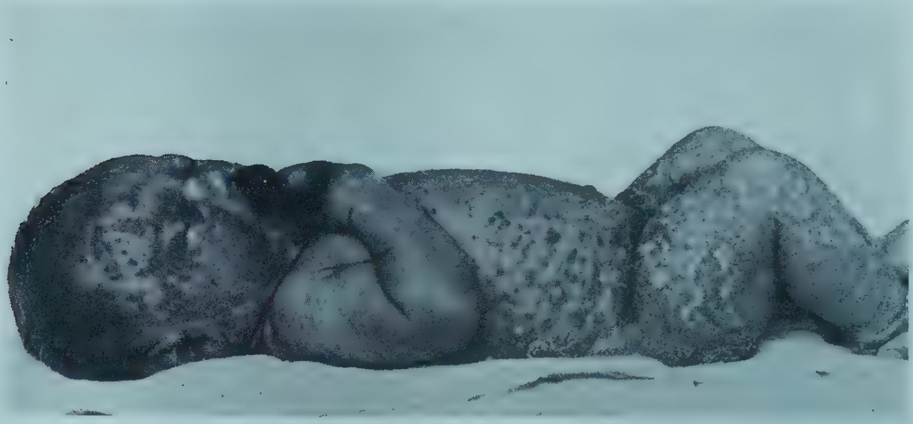

FIG. 157. ERYTHRODERMA DESQUAMATIVA (LEINER'S DISEASE)

For bottle-fed infants, Finkelstein recommends a diet poor in fat and sodium chloride, but relatively rich in protein and high in fruit and vegetables. This means that milk, as well as any other food containing animal or vegetable fat, is excluded. On the other hand, the addition of from 10 to 15 Gm. of protein powder is highly beneficial. Two or three teaspoonfuls of Aminoids (Arlington) or Parenamine (Stearns) or Amigen (Mead, Johnson) may be given. However, the infant may prove to be allergic to these products, as the writer has had occasion to observe. In older infants, butter as well as cod liver oil should be eliminated from the diet for two or three weeks in order to determine whether the seborrheic dermatitis yields to a low fat diet. Yeast should be given freely.

After the condition has begun to improve, buttermilk and cottage cheese are added to the diet; later, beef broth and even small amounts of meat may be tried.

Just why a fat-poor diet should exert such a beneficial influence, which we have often observed, has not as yet been explained. We believe that the beneficial effect may be attributable to a change in the intestinal flora.

Lastly, local treatment is also important. The seborrhea of the scalp may be treated with a sulfur cold cream:

	Gm. or Cc.	
℞ Precipitated sulfur	1.2–2.4	xviii–xxxvi
Boric acid, 1 per cent solution		
Aquaphor	aa 48.0	aa f ʒ xii
Petrolatum q.s. ad	120.0 q.s.	ad ℥ iv

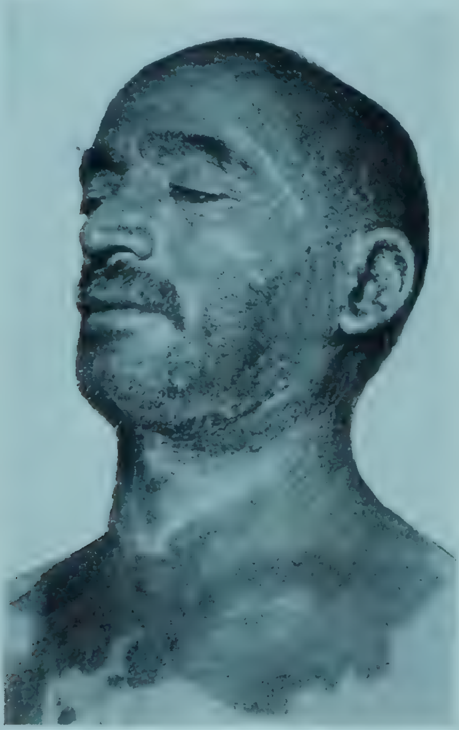

FIG. 158. SEBORRHEIC DERMATITIS INVOLVING FACE, NECK, AND UPPER PART OF THE CHEST

Seborrheic Dermatitis in Adults and Older Children

After the age of 4, the clinical picture of seborrheic dermatitis is different from that exhibited by infants and small children. Here, as in the younger patients, the lesions generally make their first appearance on the scalp, but they often extend to the ears, forehead, neck, and adjacent parts (Fig. 158). Later in life the first manifestations not uncommonly occur in the sternal regions and in the interscapular area. In severe cases other parts of the body with large and numerous sweat glands, such as the inguinoscrotal (Fig. 159), axillary, and umbilical areas (Fig. 160), also become involved. In rare instances the disease is universal (Fig. 161).

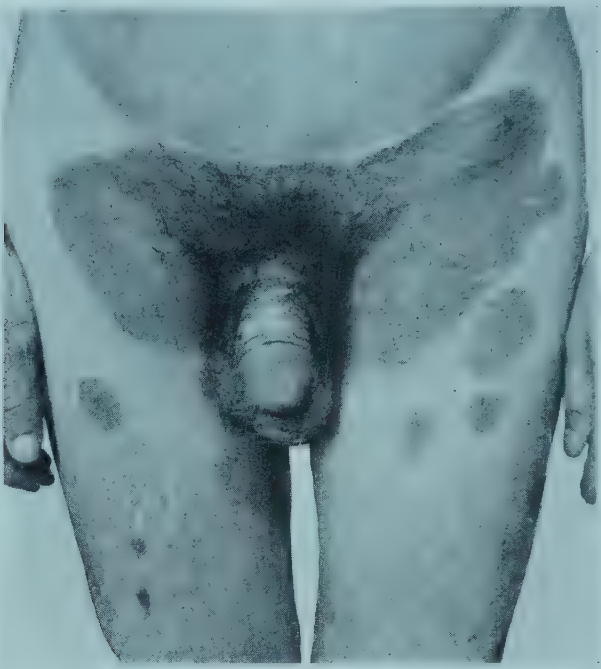

FIG. 159. SEBORRHEIC DERMATITIS OF THE INGUINAL-SCROTAL AREA

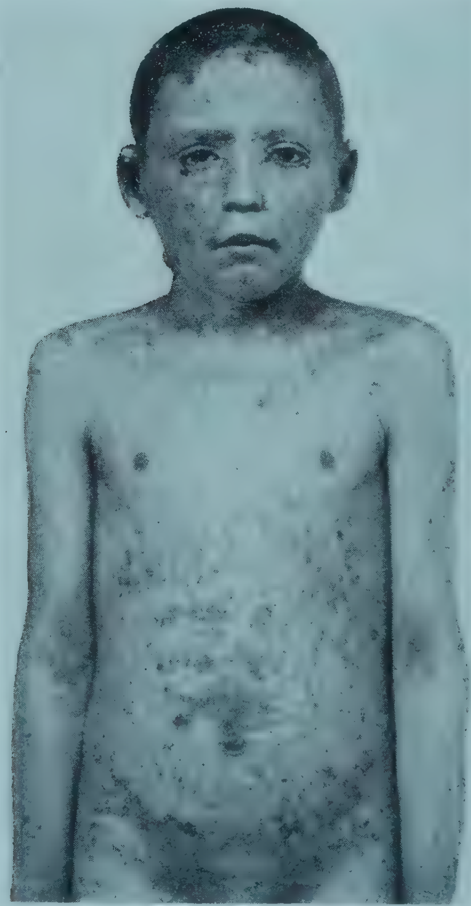

FIG. 160. SEBORRHEIC DERMATITIS OF FACE AND TRUNK

While many authors believe that this disorder is infectious in character (Moore and associates,[916] MacKee and Lewis[917]), the predisposing factors are, according to Sutton and Sutton,[337] indigestion, excessive intake of oily foods, hypothyroidism, and generally lowered vitality.

On the other hand, György[419] demonstrated that a scaly, desquamative dermatosis of the seborrheic type could be produced in rats by a diet high in raw egg white, and that the condition could be completely cured by administration of biotin. These findings were confirmed by Milbradt.[918] However, the process involved here is probably not merely a simple deficiency but depends also on the toxic effect of raw egg white on the digestive tract. Moreover, while experimental seborrheic dermatitis has some characteristics in common with seborrheic dermatitis in man, it cannot be identified with the latter because biotin has to date proved disappointing in the treatment of seborrheic dermatitis in human beings.

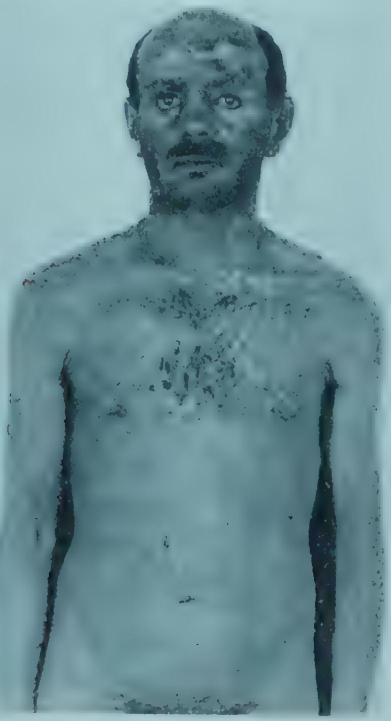

FIG. 161. GENERALIZED SEBORRHEIC DERMATITIS

Gross,[840] incriminating other factors of the B complex, found crude liver extract or the combination of thiamine hydrochloride, riboflavin, and niacin, administered parenterally, to be beneficial (Figs. 162, 163). In cases which prove resistant to liver therapy, Gross advocates correction of all phases of the diet, including a reduction of the intake of carbohydrates, fats, and total calories in the obese seborrheic patient, together with the treatment of such conditioning factors as achlorhydria, biliary tract disturbances, and diabetes mellitus. In recent years there have appeared increasingly frequent reports of the favorable influence on seborrheic dermatitides of crude liver injections (3 cc. once or twice weekly) and a diet rich in vitamin B complex and its components (see p. 167). The literature is summarized in Sayer's paper.[919]

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[916] MOORE, M., KILE, R. L., ENGMAN, M. F., and ENGMAN, M.F. JR.: Arch. Dermat. & Syph. **33:** 457, 1936.

[917] MACKEE, G. M. and LEWIS, G. M.: J. Invest. Dermat. **1:** 131, 1938; **2:** 31, 1939.

[918] MILBRADT, W.: Dermat. Wchnschr. **103:** 1376 and 1402, 1936.

Wright and co-workers[457] reported that injections of pyridoxine in doses of 25 to 100 mg. led to definite improvement and, in some instances, to complete disappearance of the seborrheic lesions in cases which had been refractory to all other measures.

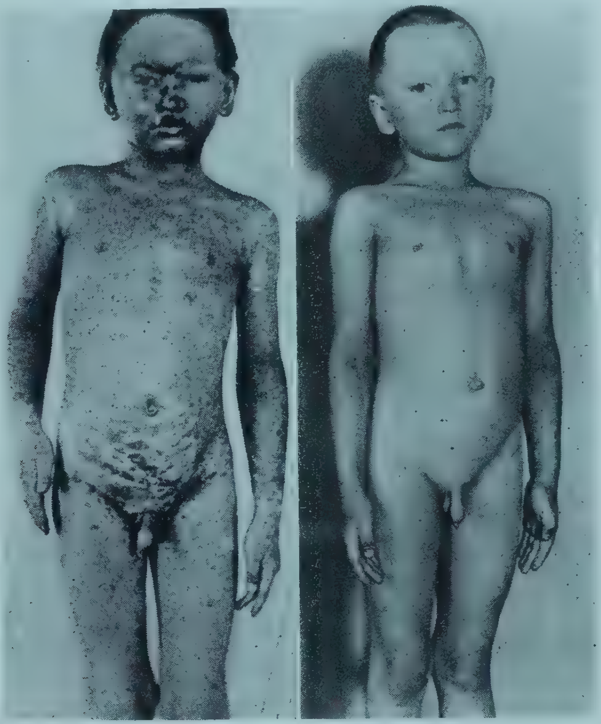

Fig. 162 Fig. 163

Effect of Liver Therapy on Seborrheic Dermatitis

Fig. 162. Before treatment.
Fig. 163. After three months of crude liver therapy.
(Courtesy of Dr. P. Gross and the Archives of Dermatology and Syphilology.)

Moreover, an infectious dermatitis may have been grafted on the seborrheic soil, and require appropriate treatment. In addition, the picture may be further complicated by the fact that the patient proves to be hypersensitive to topical applications, e.g., of sulfur and ammoniated mercury. Untoward reactions of this kind are not uncommon (Gross[840]).

In cases presenting the clinical picture of generalized seborrheic dermatitis or of exfoliative erythroderma, often arising in association with

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919. Sayer, A.: Urol. & Cutan. Rev. **46:** 719, 1942.

treatment with arsphenamine, sulfonamides, gold, and bismuth, Gross[792] assumes the presence of a complex deficiency conditioned by hepatic dysfunction. In cases presumably due to the hepatotoxic effect of chemotherapy, everything possible should be done to improve the liver function, including notably a diet high in proteins and properly regulated in regard to carbohydrate and fats, with yeast, wheat germ, and liver extract added.

Hellier[492] ventured the opinion that seborrheic dermatitis may be favored by or associated with an insufficient supply of vitamin A. In this connection it is interesting to note Manson-Bahr's observation[920] that in tropical countries hypovitaminosis A causes an unusually high incidence of intertrigo and napkin dermatitis in babies.

The treatment of seborrheic dermatitis in older children is, on the whole, similar to the therapeutic program applied to small children, namely, a low fat diet which provides for an adequate intake of protein and carbohydrate. Nevertheless, the physician must see to it that the patient gains weight normally and that any possible nutritional disturbances are corrected. Thyroid medication is often beneficial in older children with obesity and delayed puberty.

The management of seborrheic dermatitis in adults has undergone considerable change in recent years. Emphasis has shifted to low fat diet (Sutton, Jr.[921]), crude liver extract, and vitamin B complex and some of its components, as discussed above. Moreover, correction of gastrointestinal abnormalities and metabolic disturbances is of great importance.

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920. Manson-Bahr, P. H.: in Manson's Tropical Diseases. London: Cassell, 1941.
921. Sutton, R. L. Jr.: Urol. & Cutan. Rev. **43:** 670, 1939.

CHAPTER IX

Urticaria and Associated Conditions

Although urticaria and angioneurotic edema are clinically clearly distinct entities, they are often produced by the same causes. Moreover, one quite frequently encounters patients who present urticaria and angioneurotic edema concurrently. For didactic reasons, the two conditions will be discussed separately.

A. Urticaria

The term "urticaria" will be used to designate acute and chronic forms which arise spontaneously, but not urticaria factitia (dermographismus elevatus) or lichen urticatus. The latter condition is discussed separately on page 429.

The causes of urticaria are manifold. It is a great and all too common error to believe that every urticarial manifestation must, of necessity, be of allergic origin. Moreover, it should be stressed most emphatically that it is by no means enough to identify and eliminate the exciting factors, for it is often equally important to discover and, wherever possible, eradicate the predisposing factors in order to achieve a lasting cure.

The multiplicity of the causes of urticaria can be seen from Table 80, which presents a study of etiologic factors of 500 cases observed by the present writer. Only about one fourth of the total were of allergic origin, when avoidance and exposure tests, rather than skin tests, were relied upon as the basis of diagnosis. This conforms very well with the findings of Fink and Gay[922] and Hopkins and Kesten,[923] who gave the allergic classification a rating of only 20 per cent. In more than one third of all our cases digestive disorders were found to play an etiologic role. Moreover, as stressed by Stokes, Kulchar, and Pillsbury,[924] urticaria is a disease of complex rather than single causation, with regard to both the predisposing and the exciting causes. For this reason it seems necessary to consider the etiology and pathogenesis of urticaria not only from the viewpoint of this book, e.g., food allergy, gastrointestinal disturbances, and metabolism, but from a more comprehensive point of view so that the reader will be able to appreciate the complexity of the problem and be guided as to the therapeutic measures to be applied.

1. Allergic Urticaria

Countless cases have been reported in which the allergic agent was identified beyond question, either by means of avoidance and exposure

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[922] Fink, A. I. and Gay, L. N.: J. Allergy 5: 615, 1934.

[923] Hopkins, J. G. and Kesten, B. M.: Arch. Dermat. & Syph. 29: 358, 1934.

[924] Stokes, J. H., Kulchar, G. V., and Pillsbury, D. M.: Arch. Dermat. & Syph. 31: 470, 1935.

Table 80.—*Etiologic Factors in Urticaria*

Causation		Number of Cases			
		Male	Female	Both Sexes	Total
Allergic Basis					
Exogenous factors	Foods	37	62	99	
	Drugs	4	7	11	
	Injections: serum	0	3	3	
	Tuberculin	0	1	1	
	Animal stings	0	3	3	117
Endogenous factors	Autosensitization	7	7	14	
	Menstruation, pregnancy	0	9	9	23
Pathergic Basis					
Physical agents	Cold	5	22	27	
	Heat	13	4	17	
	Mechanical	17	13	30	
	Exertion		4	4	
	Light		2	2	80
Infections	Systemic	2	7	9	
	Focal	10	10	20	29
Digestive disorders	Acute gastroenteritis	18	26	44	
	Chronic gastroenteritis, colitis	35	57	92	
	Gastric anacidity	2	9	11	
	Gastric hyperacidity	2	1	3	
	Constipation	5	2	7	
	Diseases of liver, gallbladder	5	3	8	
	Alcoholism	3	1	4	169
Endocrine disorders	Hyperthyroidism	0	6	6	
	Tetany	0	1	1	7
Psychic factors		5	18	23	23
Unknown Basis					
Undetermined factors		25	27	52	52
Totals		195	305	500	500

tests or by the Prausnitz-Küstner method. Since it is not feasible for us to discuss all the possibilities in this book, we shall present a short summary according to the following outline: (a) exogenous allergens as a cause of urticaria, acting by (1) ingestion (foods, drugs), (2) injection (serum, insect stings), (3) inhalation, (4) percutaneous contact; (b) endogenous allergens as a cause of urticaria.

a. Urticaria Due to Exogenous Allergens

Ingestants. An appreciable percentage but by no means the majority of cases of allergic urticaria are attributable to hypersensitiveness to food (Figs. 164, 165, 166). Many instances of urticaria due to food allergy are cited in the section on food allergy. In order to avoid repitition we refer the reader to pages 202–76. In principle, any and all animal and vegetable proteins, as well as carbohydrates, fats, salts, and spices, can act as urticariogenic agents. In seventy-two cases it was possible to demonstrate the presence of uncomplicated hypersensitiveness to either animal or vegetable protein. In other instances, however, the mere elimination of the offending food from the diet or the administration of the indicated Propeptan was not sufficient; it was also necessary to control the coexistent anacidity or hyperacidity with appropriate diets or drugs, and to treat other gastrointestinal disturbances or infections. This procedure of simultaneously attacking the allergy-predisposing and the allergy-precipitating factors is, as yet, insufficiently employed. Failure to give due consideration to the various predisposing factors is unquestionably one of the main reasons why treatment limited to exclusion of the

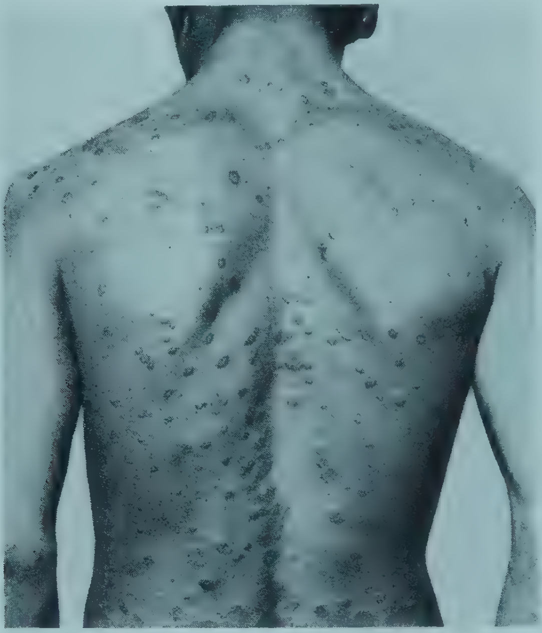

FIG. 164. URTICARIA DUE TO HYPERSENSITIVENESS TO MUTTON

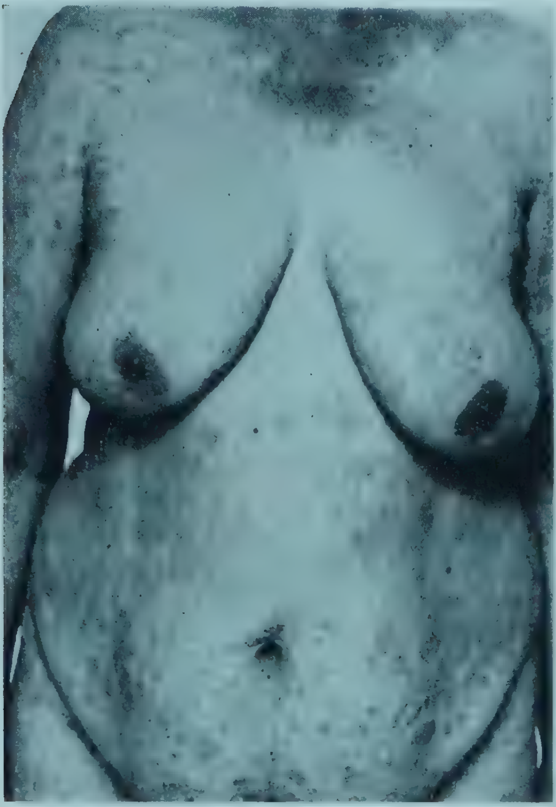

FIG. 165. URTICARIA DUE TO HYPERSENSITIVENESS TO BEEF

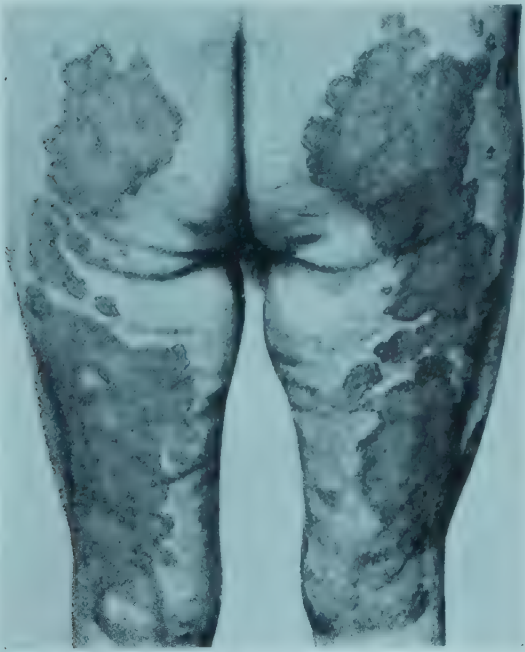

FIG. 166. URTICARIA DUE TO HYPERSENSITIVENESS TO STRAWBERRIES

given nutritive allergen or to administration of Propeptans is bound to fail.

As shown by the ingenious experiments of Rappaport and Hoffman,[925] urticaria can also be caused by the nonprotein components of foods, such as the aliphatic unconjugated aldehydes produced by the oxidation of fatty oils in the frying of foods and absorbed by the intestinal tract.

Drugs taken by mouth can likewise, although far less commonly than foods, bring on urticarial manifestations. For details, the reader is referred to the author's text on allergy.[26]

Injectants. That injection of foreign serum elicits urticarial manifestations constitutes a well known phenomenon as seen in serum sickness. Similarly, many individuals react with local and sometimes even extensive wheal formation to insect stings and bites (bee, wasp, flea, bedbug, etc.). Furthermore, insulin, liver (Fig. 167), and other organ extracts not uncommonly evoke hives; sometimes, however, the eruption is caused by the oily vehicle in which the active principle is dissolved. Moreover, urticarial manifestations have been observed after subcutaneous and intramuscular injections of a great variety of drugs.

TABLE 81.—*Exciting and Predisposing Factors in Urticaria Due to Foods*

Exciting Factors	Predisposing Factors	Number of Cases		
		Male	Female	Total
Proteins	Not determined	29	43	72
	Gastric anacidity	2	6	8
	Gastric hyperacidity	2	0	2
	Gastroenteritis	4	9	13
	Tonsillitis	0	2	2
Carbohydrates		0	2	2
Total		37	62	99

Urticarial lesions appearing either during or immediately following blood transfusions may, of course, be due in some instances to passive transfer of the donor's antibodies. On the other hand, the donor's blood may contain traces of food proteins to which the recipient is hypersensitive. Thus, Stewart and Bates[926] reported a case in which the donor had eaten cockles the night before giving a transfusion to a patient who, it developed, was markedly hypersensitive to any type of shellfish.

Inhalants. The significance of inhalant allergens in the production of hives has not as yet been fully appreciated. On page 237 food odors as a cause of urticaria, angioneurotic edema, and other dermatoses are discussed and pertinent literature appended. Here we shall only cite a case, observed by us, who was so extremely hypersensitive to fish that merely smelling that food caused the appearance of severe urticaria. Other agents outstanding among these inhalants are feathers, cotton, kapok, silk, various kinds of dust, flour, animal danders, pollen, orris root, the scents of flowers, nasal sprays (including ephedrine), insecticides, dyed materials, and chemicals, such as paraphenylendiamine. It appears likely that inhaled substances are absorbed through the respiratory tract and then distributed hematogenously to the skin. A case reported by Rusk and his associates[927] is particularly interesting and enlightening: urticarial manifestations occurred when glycerin-treated cigarettes were smoked, and the patient was found to be hypersensitive to acrylaldehyde formed as a by-product during the burning of the cigarettes. Vaughan[588] observed a woman who developed urticaria when smoking or even on entering a room where others were smoking.

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[925] RAPPAPORT, B. Z. and HOFFMAN, M. M.: J. A. M. A. **116**: 2656, 1941.

[926] STEWART, W. and BATES, T.: Lancet **1**: 319, 1938.

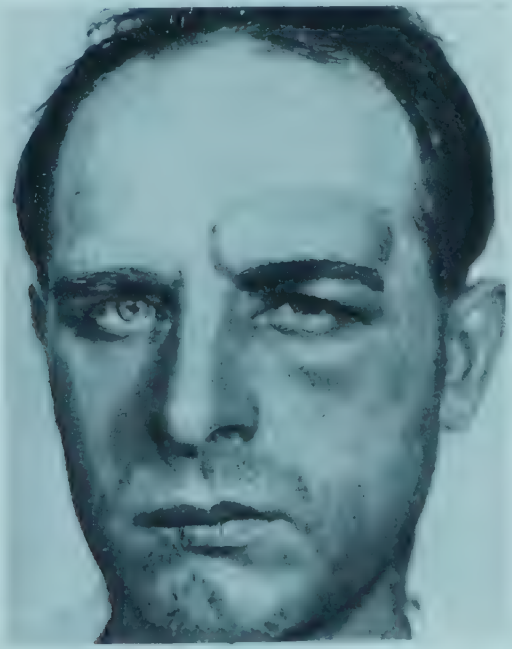

Fig. 167. Urticaria Due to Hypersensitiveness to Liver

Contactants. Although urticaria is fundamentally due to hypersensitiveness of the cutaneous blood vessels, it is important to bear in mind that it may be elicited in rare cases by epidermal contact with certain agents. It may well be that substances so applied reach the cutaneous blood vessels by way of the cutaneous lymph channels. However, contact with foods rather infrequently evokes urticaria. Thus the present writer has observed hives in three patients due to contact with lemon peel proved to be caused by the ethereal oil in the lemon skin. Joltrain, Brabant, and the author have each observed cases of urticaria of the hands caused by contact with egg white.

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[927] Rusk, H. A., Weichselbaum, T. E., and Somogyi, M.: J. A. M. A. 112: 2395, 1939.

b. Urticaria Due to Endogenous Allergens

The writer is convinced that endogenous allergens play a considerable part in the causation of urticaria. A distinction should be made between auto-endogenous and hetero-endogenous allergens. The former are understood to include blood or tissue protein that has been rendered foreign to the body and has thus become an endogenous allergen capable of eliciting an urticarial reaction. This heterogenization of the protein is usually a result of operation, scalding, traumatic sanguinous extravasation, or other physical injury. In view of the very great number of operations and accidents that take place, and in view of the fact that urticarial cases of this kind are only rarely encountered, it must be concluded that the organism produces antibodies to autogenous protein only under very special conditions. Particularly worthy of note in this connection is a case seen by the writer: urticaria which had stubbornly resisted all therapy disappeared on the very day on which a hitherto undiagnosed hydatidiform mole was found in the patient and removed. According to Joltrain,[602] this category might also include cases due to as yet only vaguely defined products of fatigue formed in the tissues in the course of physical overexertion, and making their way into the blood stream. Urticarial conditions sometimes arise in association with processes involving extensive cell disintegration, such as gout or lymphogranulomatosis.

2. PATHERGIC URTICARIA

As pointed out in the introductory paragraphs of this section, urticaria is by no means always based on an allergic mechanism. However, it is always the expression of an abnormal hypersensitiveness to internal and external agents. Since the present author[26] uses the term "pathergy" to denote every hyper-, hypo-, and insensitiveness in which, at least at present, an antigen-antibody mechanism cannot be demonstrated, he suggests the use of the term "pathergic urticaria" in order to distinguish it from "allergic urticaria."

We shall now enumerate the pathologic conditions and abnormal metabolic processes often found in connection with urticaria. It is necessary in each case to conduct appropriate studies to determine whether they are the exciting factors acting by means of their toxic products, or whether, as is very frequently the case, they are the predisposing factors in addition to which a "trigger" mechanism must become operative in order to induce urticaria.

Gastrointestinal Diseases

Here we must distinguish between a number of different conditions. In occasional instances, hyperacidity is the only cause of urticaria, as shown by the prompt disappearance of the cutaneous manifestations after appropriate dietary and therapeutic management, and by reappearance of the urticaria when the acidity again rises (Dobreff and Popchristoff[744]). A far more common cause, however, is marked hypo-acidity or anacidity. In such cases, not only the lack of hydrochloric acid but also the resulting changes in the chemistry and flora of the intestine are of importance. In still other, and by no means uncommon, cases abnormalities of the gastric acidity are the predisposing factors in hypersensitiveness to food. This should be borne in mind, because adequate treatment requires not only management of the secretory disturbance or of the nutritive allergy alone, but also measures designed to combat both factors (see p. 295).

The next and much larger group of conditions comprises gastritis and enteritis. Both the acute and the chronic forms are of great importance. Acute enteric processes, usually caused by food poisoning and characterized by nausea, vomiting, generalized abdominal pain, diarrhea, and marked malaise, are often followed by urticaria. The latter may be induced by the toxins themselves or by resorption of tissue protein altered as the result of the damage to the gastrointestinal mucosa, or by absorption of undigested or partially digested food through the inflamed lining membrane. In this connection it should be mentioned that severe attacks of urticaria are frequently brought on by overindulgence in alcohol, causing gastritis and enteritis, and thus furthering resorption of insufficiently digested food protein. An even larger number of cases is based on chronic irritation of the gastrointestinal tract. The fact that chronic enteritis can be the underlying cause of hives has received scant attention and is, indeed, little known (Fig. 168). This disease picture manifests itself by the presence of numerous fatty acid crystals and soapy globules in the stool, as well as by rapid elimination of the barium meal, which in these cases reaches the large intestine in about two hours. Good therapeutic results can be obtained by adherence to a bland diet consisting essentially of milk and free of all cellulose-containing foods (see Table 68, on p. 321).

Another condition to be included here is colitis, which may be a cause of intestinal putrefaction and fermentation. What has been said about gastritis applies equally to colitis: namely, in some instances the eradication of the intestinal disease may, in itself, serve to put an end to the urticarial condition (Fig. 169). In other cases, however, the mechanism is somewhat different. Incompletely digested food proteins may be resorbed through the inflamed colonic mucosa, thereby allergizing the organism; hence, when adherence to an appropriate colitis diet does not

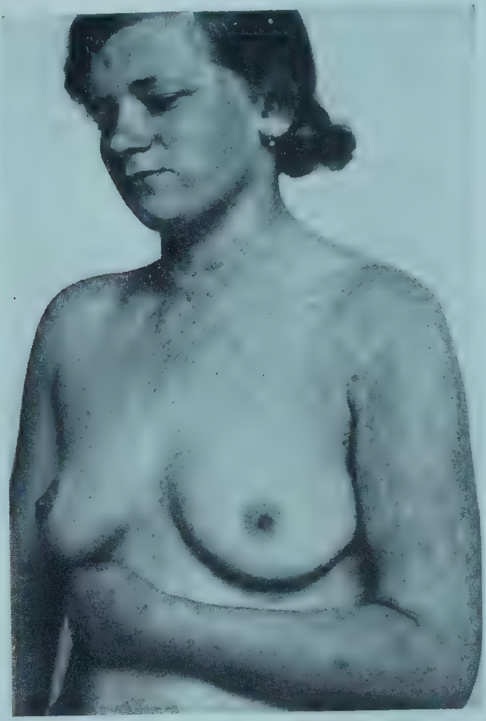

FIG. 168. URTICARIA ON THE BASIS OF ENTERITIS

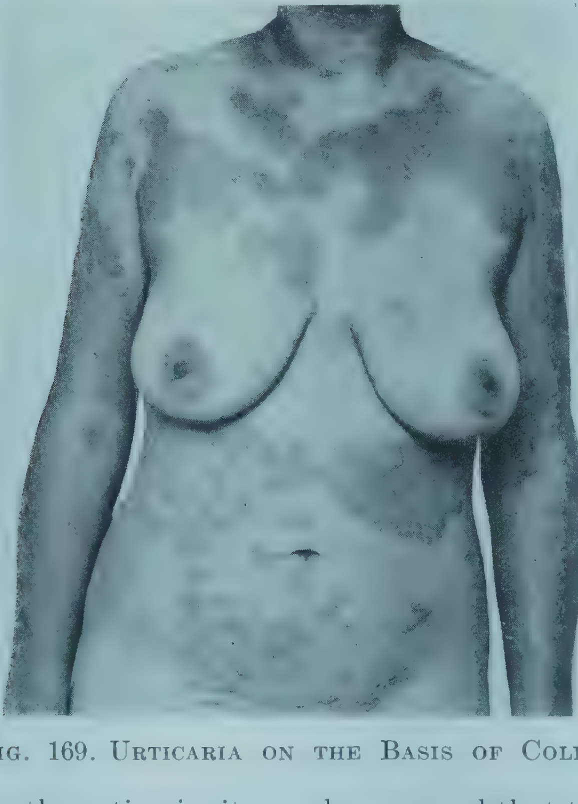

FIG. 169. URTICARIA ON THE BASIS OF COLITIS

suffice to clear up the urticaria, it may be assumed that there is also a food allergy that may be controlled, for instance, by specific Propeptans (Fig. 170).

Finally, urticaria may involve the gastric mucosa itself, as reported by Chevalier.[746] Gastroscopy in these cases revealed changes varying from acute edema to local or generalized atrophic gastritis. In his opinion, the cutaneous and the mucosal manifestations are frequently concomitant symptoms produced by a single agent.

Furthermore, constipation is to be considered among the intestinal diseases, and attempts should be made in every case to correct it by means of an appropriate regimen. A decision as to whether constipation plays a role in a case of urticaria can be quickly reached by observing the results of colonic irrigations. Sometimes, however, the latter procedure may be followed by a rather violent although transitory outbreak of hives, presumably due to the increased absorption of the noxious agents by the mucous membrane.

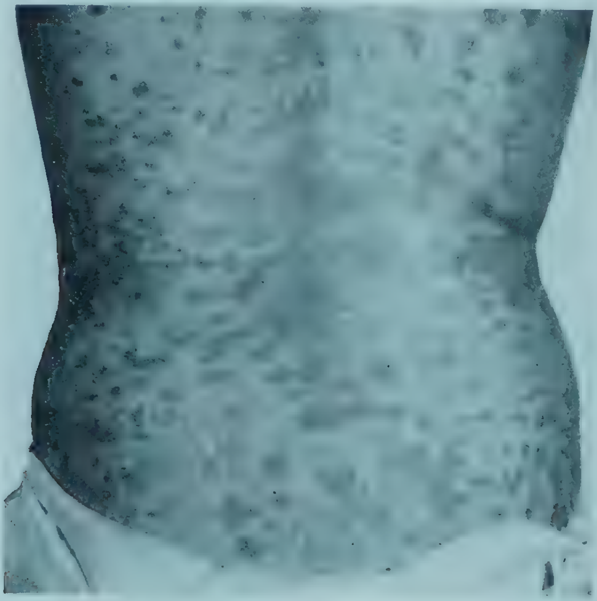

FIG. 170. URTICARIA DUE TO WHEAT ALLERGY BUT APPEARING ONLY DURING ATTACKS OF COLITIS

In occasional instances urticaria may be attributable to pancreatic insufficiency. Thus, Markel[846] reported a case in which treatment consisting only of oral administration of insulin-free pancreatic extract brought relief from symptoms. For years the present writer has been treating similar cases with large doses of hydrochloric acid, pepsin, and pancreatin. If the skin manifestations disappear, the pancreatin is omitted in order to determine to what extent the pancreas is involved in the cutaneous symptoms.

Liver and Gallbladder Diseases

In a number of cases of refractory urticaria, Shay,[798] Schur,[794] Daniel,[797] Urbach,[26] and others found diseases of the liver and/or gallbladder, appropriate treatment of which resulted in cure of the cutaneous condition. According to Shay, as well as Daniel, Decholin is especially useful. We must not fail to mention, however, that in our experience some cases of liver and gallbladder disease, manifested on the one hand by icterus and on the other by biliary colic, are not the underlying causes of urticaria, but rather additional clinical expressions of the same mechanism. An instance of urticaria and severe gallbladder crises, which could be evoked by ingestion of lobster, has been fully described by the present author[26] with roentgenograms of the gallbladder. In another patient, jaundice became manifest eight days after the urticaria first appeared.

Diseases of the Urinary Tract

Conditions of the urinary apparatus, particularly of the kidney and renal pelvis, and also of the bladder, may cause urticaria, either directly or as a result of secondary infection.

Diabetes Mellitus

Of all the metabolic diseases, diabetes mellitus is the most frequently overlooked cause of occasional cases of chronic recurrent urticaria. Such an oversight is especially likely when the urine is negative for sugar and the fasting blood sugar level is normal. Whenever the etiology of urticaria is obscure, a glucose tolerance test should be performed. However, there are a few cases in which the skin carbohydrate tolerance, as demonstrated by an increased cutaneous sugar content, is impaired despite normal blood sugar curves (see p. 34). Since the determination of skin sugar levels can be carried out only in specially equipped laboratories, a simple clinical test may be substituted. This consists of having the patient adhere briefly to a strict diabetic diet (three to four days), combined with administration of small doses of insulin (5 units subcutaneously, three times daily). If the urticaria disappears after this procedure, the presence of "skin diabetes" may be assumed. It is interesting to note that this condition is chiefly found in persons over 45 years of age, characterized by a peculiar purplish color of the cheeks and by obesity, and likely to be of the Jewish race. Proceeding in this way, the writer[36] succeeded in curing a number of previously refractory cases of chronic urticaria.

Gout

Occasional cases of urticaria have been found to be due to gout. In one instance the writer, by means of uric acid determinations in the blood and skin, succeeded in bringing definite proof to this effect.

Disturbance of Acid-Base Equilibrium

A number of authors, headed by Schreus,[146] hold that a fair percentage of all cases of urticaria are due to disturbances of the acid-base equilibrium, particularly acidosis. Without entering into a discussion here as to whether these metabolic disturbances are primary or coordinate we can state that in our own experience, as well as in that of von Noorden and Salomon,[319] Dinkin,[928] McCaskey,[929] Luckner and Mann,[930] Vallery-Radot,[931] and others, alkaline therapy is frequently very useful and sometimes even effects a permanent cure. This classification also embraces the so-called sweat urticaria of Marchionini and Ottenstein.[932] In this condition hives are evoked by profuse sweating, and an attack can also be elicited by an injection of pilocarpine. Alkalinizing diets (see p. 55) are likewise beneficial here.

Endocrine Disturbances

These play an important role in urticaria, particularly in women. The possible influence of the menopause, as well as of menstrual disturbances (amenorrhea, dysmenorrhea), must be considered, and the indicated substitutional therapy should be instituted to correct them. Furthermore, tests of thyroid function must be performed on patients of both sexes, since hyperfunction of the thyroid gland is not rarely a factor, at least in promoting allergy. The writer has repeatedly observed that hyperthyroid patients tend to suffer severe attacks of hives, and that often these urticarial attacks do not cease until the thyroid disease is cured. It is interesting to note that in two of our cases the first urticarial manifestations made their appearance after roentgen irradiation of the thyroid gland. This is probably to be interpreted as an expression of allergization brought on by altered thyroid proteins acting as endogenous allergens. Loew, however, has reported the appearance of urticaria and angioneurotic edema following thyroidectomy, with a postoperative basal metabolic rate of minus 12; the cutaneous manifestations responded favorably to the administration of 1 mg. of thyroxin, and reappeared when this medication was interrupted. We observed a case in which a severe attack of urticaria followed the inadvertent removal of the parathyroids during thyroidectomy; the urticarial condition failed to manifest itself as long as parathyroid hormone was administered.

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928. Dinkin, L.: Med. Klin. **26:** 1921, 1930.
929. McCaskey, G. W.: J. Lab. & Clin. Med. **7:** 534, 1922.
930. Luckner, H. and Mann, E.: Klin. Wchnschr. **18:** 767, 1939.
931. Vallery-Radot, P., Blamoutier, P., Claude, F., and de Lavedon de Casanbon, A.: Bull. et mém. Soc. med. d. hôp. de Paris **53:** 390, 1937.
932. Marchionini, A. and Ottenstein, B.: Klin. Wchnschr. **10:** 969, 1931.

It is certain that the development of urticaria is dependent upon a lability of the neurovegetative system; the manner in which imbalances of this system occur may, of course, vary from case to case. This explains the far higher incidence of urticaria among adults than among children; its relatively greater frequency among women than among men; the commonly observed association of urticaria with angioneurotic edema and migraine, especially in women; and the well known dependence of urticaria, of whatever origin, on menstruation, emotional upsets, and similar factors.

Bacterial Infections

Another group of conditions of etiologic importance in the production of urticaria are the infections. These should be divided into general and local types. Those which are general, influenzal and rheumatic infections, are to be regarded as paving the way for, rather than actually causing, urticaria. The question as to whether the urticariogenic influence of the infections is based on toxicity or allergy has not as yet been answered. The situation is all the more obscured by the fact that, especially in acute infections, the results of skin tests with bacterial substances are very frequently negative.

Focal infections, however—particularly in the tonsils, sinuses, and teeth, as well as in the appendix, gallbladder, bladder, cervix, and elsewhere—frequently constitute the only etiologic factor; and the removal of such foci effects a rapid and lasting cure of the urticaria. Fuld[933] and Leriche[563] reported a number of patients with urticaria which was controlled by removing an infected appendix. Oberndorf had the same experience with a case of angioneurotic edema. Where the etiology is uncertain, the possibility of hypersensitiveness to pathologic intestinal bacteria must be considered, and appropriate investigative measures, sometimes including tests with autogenous stool vaccines, must be undertaken. In short, every case of urticaria should be carefully investigated (by specialists, whenever necessary) for any possible focus of infection. To minimize the possibility of overlooking any such focus, we present Table 82 on page 421.

Needless to say, the existence of focal infection in the presence of urticaria does not necessarily prove that the former plays a causal role. Nevertheless, it is always advisable to eliminate such a focus when conservative measures prove inadequate and when surgical intervention is not contraindicated. One must not expect, however, that eradication of the infection, even when it is the cause of the urticaria, will bring immediate results, especially in cases in which it is the allergy-predisposing and not the allergy-producing factor. It is advisable in every case to prepare an autogenous vaccine from the focus and to inject it at intervals of from three to five days. A renewed and severe attack of urticaria is not infrequently observed after incision of a suppurative focus or surgical removal of an infected organ; however, if this infection was the cause, no further attacks of urticaria will ensue.

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[933] Fuld, E.: in Verhandl. f. Verdauungs- u. Stoffwechselkr. 5th Tagung 1925.

In cases in which infection of the intestinal tract can be bacteriologically proved, it is advisable to administer an autogenous stool vaccine. Good results by this method have been reported by Emmet and Logan,[934] Hopkins,[935] and Traut.[936] Cultures from duodenal drainage are occasionally useful (Hansen-Pruess[799]).

TABLE 82.—*Sites of Focal Infections*

Eyes: dacryocystitis
Ears: infection of external auditory canal, otitis media
Sinuses: frontal, maxillary, ethmoids, sphenoids
Teeth: pyorrhea alveolaris, periodontal pocket, periodontitis
Pharynx: adenoids, tonsils
Bronchi: bronchitis, bronchiectasis
Gastrointestinal Tract: gastroenteritis, appendicitis, colitis, proctitis, dysbacteria (abnormal intestinal flora)
Gallbladder: cholecystitis
Urinary Tract: pyelonephritis, cystitis, urethritis
Genitalia: prostatitis, vesiculitis, endometritis, endocervicitis, salpingitis, oophoritis
Bones and Joints: osteomyelitis, infectious arthritis
Skin: pyodermia, paronychia (fingers, toes), fungous infection

Systemic Diseases

In some cases it is impossible, despite the most painstaking investigation, to determine the cause of urticaria. Sometimes, especially when the patient steadily loses weight, the possibility of cancer must be borne in mind. In other instances urticaria is a premonitory symptom of pernicious anemia or of disease of the hematopoietic system (leukemia, lymphogranulomatosis).

Psychic Factors

Psychic influences are rather frequently the underlying cause of urticaria. Stokes, Kulchar, and Pillsbury,[924] who investigated the pathomechanism of urticaria in a large number of cases from all possible angles, found that in 12 per cent of these psychoneurogenous disturbances were

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934. EMMETT, J. L. and LOGAN, A. H.: J. A. M. A. **101:** 1966, 1933.
935. HOPKINS, J. G.: New York State J. Med. **38:** 23, 1938.
936. TRAUB, E. F.: Arch. Dermat. & Syph. **40:** 368, 1939.

the only responsible factor, and such influences played at least a contributory role in no less than 83 per cent.

A distinction must be made between various types of psychogenic mechanisms. There is not the slightest doubt in the mind of any clinician that hives are influenced by worry, excitement, and other emotional upsets. However, this sort of emotional background is not under consideration here. We are referring to those cases in which, to all appearances, the psychic trauma constitutes the only etiologic agent. It is to be noted in this connection that the psychogenic element is more important in women than in men. Obviously, it is not easy to find definite proof of the fact that a case of urticaria is due solely to an inner conflict. In some instances of heat urticaria, any emotion may bring on renewed attacks of hives; under such circumstances the psychic element cannot be considered as the primary cause of the urticaria, since it operates by way of its effect on the heat-regulating mechanism. Moreover, there are not rarely seen patients in whom, as a result of psychologic conditioning, the primarily allergic urticaria persists long after exposure to the excitant has ceased.

But even when consideration is given to all these possibilities, there remain cases which may be regarded as psychogenic in origin. The writer has had occasion to observe a number in which previously refractory urticaria disappeared after the settlement of a grievance, or after changes in certain psychic conditions. It is noteworthy that these patients in particular attempt to dissemble and to deny the existence of a psychic factor. Thus, the writer observed the case of a highly intelligent but distinctly masculine woman whose chronic urticaria persisted stubbornly until she finally decided to break her engagement. Another pertinent example was that of an elderly man who had hives as the result of grief over his sons' neglecting him; many weeks of intensive treatment were of no avail. Finally, after a frank discussion of the situation, followed by a change in attitude on the part of his sons, the old man's condition rapidly improved and was soon cured. Careful investigation to determine the nature of the psychic background and an explanation to the patient of the relationship between emotional disturbances and urticaria are more likely to bring relief than is a purely allergic approach followed by treatment along the usual lines.

Physical Factors

In our material, a strikingly high percentage of cases fall under the classification of urticaria due to hypersensitiveness to physical agents. Although somewhat surprising, this may be explained by the fact that in every one of these cases, regardless of whether the history seemed to call for them, systematic tests were performed for hypersensitiveness to cold, heat, sweat, pressure, exertion, and light.

Although urticaria due to physical stimuli is sometimes of allergic origin, there are many instances in which allergy seems to play no part whatever. There are cases in which the cure of gastric disease or of enteritis, the elimination of focal infection (such as a granuloma of a tooth, tonsillitis, or appendicitis), of worm infestation, or of endocrine disturbance, is promptly followed by cessation of the urticaria due to cold, pressure, or other agents. Cases of this kind, as well as those in which there is no specific reaction to one physical factor, although the patient reacts with wheal formation to any number of different physical stimuli, should in our opinion be considered as vasoneuropathies, i.e., as nonspecific vascular responses. Needless to say, the differentiation between allergic and nonallergic causation in a given case of urticaria due to physical stimuli is of decisive importance from the therapeutic point of view. It should be noted, however, that even in proved allergic cases of physical urticaria, in addition to specific antiallergic measures the therapy must include the elimination of the factors predisposing to allergy (infections, toxic states, gastro intestinal disturbances, liver damage, functional imbalance of the endocrine glands, psychic trauma).

Finally, in two cases of the present writer's, food allergy was the predisposing factor for the physical urticaria. After the respective food allergens (egg in the first, and oranges and grapefruit in the second instance) were controlled by the appropriate Propeptans, cold water no longer induced urticaria.

3. Etiologic Diagnosis

It is apparent from the diversified pathogenesis of urticaria that there can be no one method of determining the cause in any given case. One is therefore confronted first of all with the problem of ascertaining whether a case is due to an underlying allergy or to pathergy. It is often very difficult to answer this question; yet every effort must be made to do so, since the therapeutic procedure will depend upon the recognition of the true nature of the pathogenesis.

As in all allergic conditions, a minutely detailed history must be taken; this frequently puts the physician on the right track, or at least gives him some point of departure for further investigation. However, when no enlightening information is forthcoming,;the physician must systematically, point by point, look for any and all possible causes in the manner described in detail in the preceding pages. When necessary, all the resources of modern internal, allergic, and chemical investigative methods should be employed; when no clues are available, one must attempt to arrive at a diagnosis *ex juvantibus* by surgical removal of any suspicious focus.

When underlying allergy is suspected, one must avoid putting too much faith in the results of skin tests. The writer emphatically agrees with Sulzberger and Rostenberg[937] in rating all forms of skin tests as of very little value. Stokes and his associates[924] found the scratch test to be unreliable in 50 per cent of their cases. Hopkins and Kesten[938] arrived at a similar conclusion; they even found that in one large group, consisting exclusively of patients hypersensitive to foods, the ratio of dependable results was no greater than 10 per cent or, at the most, 20 per cent. Waldbott and Ascher[939] reported reactions in only 27 per cent of their cases. This may perhaps be explained by the fact that urticaria is often evoked not by the suspected substance itself, but by one of its metabolic products or derivatives, or, in other instances, by the fact that the primary shock organ is not the skin but the mucous membrane (e.g., of the gastrointestinal tract). This is why the elimination diet and particularly the Propeptan test diet (p. 251) are far more successful than skin tests in food allergies.

4. Therapy

In view of the diversity of the etiologic factors, there can obviously be no one standard therapeutic approach to urticaria. It is equally apparent that therapy must be individualized according to the indications found by painstaking investigation of a case.

SPECIFIC THERAPY

When there is a known allergenic food factor every effort should be made either to eliminate exposure to it, or, preferably, to deallergize the patient by means of a Propeptan diet (p. 267). Furthermore, regardless of whether the allergen has been identified, every case should be carefully studied for the possible presence of allergy-predisposing conditions; if such factors are found, they should, of course, be appropriately managed by either medical or surgical measures. Stokes[924] pointed out that attention to several factors in a case, rather than to one alone, increases the proportion of good results

a. Acute Cases

An attempt should always be made to empty the entire intestinal tract by means of castor oil and either a high enema or, preferably, a high colonic irrigation. Furthermore, if an infectious intestinal element is suspected, the patient should take creosote carbonate (20 drops) together with activated charcoal (1 to 2 Gm., or 15 to 30 grains) three times daily for a period of several days. The diet should be bland; coffee, tea, and alcohol are to be avoided. To control intense pruritus or severe attacks of urticaria, it is advisable to administer 0.25 to 0.50 cc. (4 to 8 minims) of 1 : 1,000 epinephrine and, if the relief is too evanescent, a series of intravenous injections of 10 per cent calcium gluconate. Pituitrin by injection sometimes gives amazingly good results, but usually only temporary. Atropine sulfate (0.25 mg. or 1/240 grain), injected subcutaneously, may well be tried. Venesection of 300 to 500 cc. is indicated if there are unbearable itching and severe headaches. Local treatment consists of the application of shaking lotions containing Anesthesin (approximately 2 to 3 per cent) or 5 per cent of Calmitol liquid:

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[937] Sulzberger, M. B. and Rostenberg, A. Jr.: J. Allergy **6:** 448, 1935.

[938] Hopkins, J. G. and Kesten, B. M.: Arch. Dermat. & Syph. **29:** 358, 1934.

[939] Waldbott, G. L. and Ascher, M. S. J. Allergy **9:** 584, 1938.

	Gm. or Cc.	
℞ Anesthesin	3.6	Gr. 1
Zinc Oxide		
Talcum	aa 24.0	aa ℥ vi
Glycerin		
Alcohol 70 per cent	aa q.s. ad 120.0	aa q.s. ad f℥ iv

Prolonged lukewarm baths containing bran or starch often give temporary relief.

b. Subacute and Chronic Cases

In addition to those just mentioned, the following measures may be useful here.

Even when a nutritive factor cannot be demonstrated, various diets are well worth trying in succession, devoting one week to each. In the first week a strict Propeptan diet; second week, a regimen completely free of animal protein; third week, a completely salt-free dietary; fourth week, an alkalinizing regimen (Table 13 on p. 55), supplemented by daily intravenous injections of 20 cc. of a 4 per cent sterile solution of sodium bicarbonate, may be tried. During the fifth week, an acidifying diet may be tried (see Table 11 on p. 53), together with 1 Gm. (15 grains) of ammonium chloride five times a day, or 0.33 Gm. (5 grains) of potassium chloride in 8 ounces of water three times a day. Eller and Rein[188] found the equilibrated salt diet (p. 67) useful. Since urticaria of digestive origin is often accompanied by localized or diffuse atrophic gastritis which may be ameliorated by large doses of iron, Chevalier and Moutier[746] advise reduced iron or ferrous carbonate after meals, increasing slowly from 3 Gm. to 6 Gm. daily, and given over a long period of time. In addition to iron, hydrochloric acid should be taken before each meal.

Occasionally, good results are obtained by changing the intestinal flora by means of Bacillus acidophilus milk or a series of colonic irrigations containing activated charcoal. If the reaction of the stool is alkaline, buttermilk (500 cc.) and lactic oats are indicated (Aitken[940]).

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[940] AITKEN, R.: Brit. J. Dermat. **51:** 13, 1939.

Autohemotherapy, 10 cc. given intramuscularly twice weekly, or autoserotherapy, 0.2 cc. injected intramuscularly on alternate days, should be tried in all refractory cases, particularly when there is reason to suspect the presence of endogenous allergy. Similarly, autogenous urine and the urinary proteoses have occasionally been found to be effective.

Cherfils[941] recommends roentgen irradiation of the spleen in a series of three to five treatments, to be repeated at increasing intervals (single dose, 250 r, with filter of 0.5 copper plus 1 aluminum). Strangely, the coagulability of the blood is increased under the influence of irradiation; moreover, Cherfils claims that the treatment has no therapeutic value unless this change appears.

In all cases of urticaria in which the patient's sleep is disturbed, effective soporifics may be given (provided, of course, that hypnotics do not appear to be contraindicated by the history) as well as sedatives to be taken during the day, such as Bellergal (1 tablet) or phenobarbital (0.015 to 0.030 Gm., or 1/4 to 1/2 grain), three times a day. In refractory cases, small doses of ephedrine (0.025 Gm., or 3/8 grain) along with phenobarbital (0.008 Gm., or 1/8 grain), given three times a day over a period of weeks, may bring lasting relief; and excellent results have occasionally been obtained with gynergen (1 tablet of 1 mg. twice a day).

That the psyche of the patient merits special consideration in urticaria has already been mentioned; a change in environment, especially a vacation in the mountains, is often beneficial.

B. ANGIONEUROTIC EDEMA

The typical form of this disease entity is characterized by a sudden and rapid development of one or more circumscribed, usually pale swellings in the subcutis, without appreciable subjective symptoms; however, the clinical picture often varies considerably from case to case, depending on differences in the site and intensity of the eruption, duration of the attacks, and intervals between them.

The localization of angioneurotic edema is usually on the face, particularly on the eyelids; however, any other skin area can be affected. Most to be feared is involvement of the mucosa, above all in the larynx, where the edema can assume such proportions that tracheotomy may become necessary.

As to the question of etiology, it must be stressed that not every case of angioneurotic edema is by any means of allergic origin. In this respect the condition is comparable to urticaria, and the reader is therefore referred to the section on the etiology and pathogenesis of the latter (p. 408). In a representative group it will be found that angioneurotic edema can be primarily caused by a number of different internal diseases, including those of the gastrointestinal tract, liver, and gallbladder. Severe constipation has also to be included in this group (Staehelin[942]). In other cases therapeutic results can be obtained by control of infectious foci—for example, removal of chronically diseased tonsils, or surgical drainage of infected sinuses (Barber,[943] Urbach). Whether the favorable results are due to the elimination of bacterial antigens or of toxins is often difficult to decide.

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[941] Cherfils, J.: Tr. 4th Internat. Radiol. Cong. 2: 330, 1934.

Nervous influences as well as peculiar predisposition of the neurovascular system certainly are of great importance. In this connection, Wilder's report[944] of the edema appearing as a result of posthypnotic suggestion may be cited.

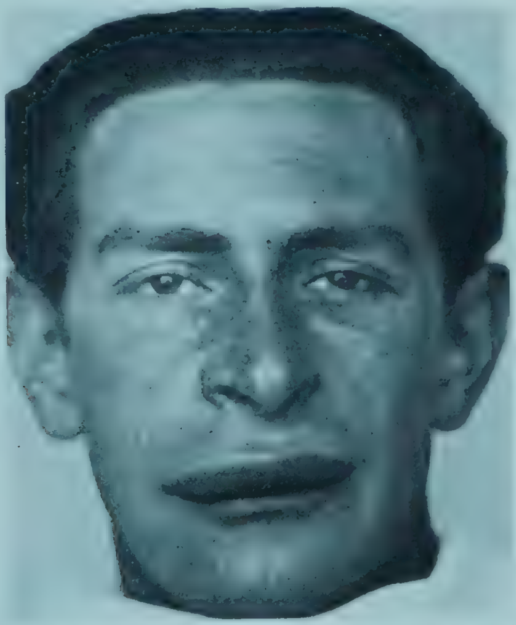

FIG. 171. ANGIONEUROTIC EDEMA OF UPPER LIP DUE TO FISH HYPERSENSITIVENESS

However, numerous cases of angioneurotic edema have unquestionably been proved to be of allergic origin. Thus, Turretini[945] reported an instance in which the condition regularly appeared following ingestion of small quantities of bread or of other foods containing flour. Lésne and Lévy[946] described a case due to raw horse meat, Phillips[947] due to pork, Maxwell[948] due to smoked fish, Sticker[581] due to duck eggs. De Besche[949]

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942. STAEHELIN, R.: Charite-Annal. **34:** 184, 1910.
943. BARBER, H. W.: Brit. J. Dermat. **35:** 209, 1923.
944. WILDER, J.: Med. Klin. **25:** 24, 1929.
945. TURRETINI, M.: Bull. et mém. Soc. méd. d. hôp. de Paris **46:** 811, 1922.
946. LÉSNE, E. and LÉVY, M.: Bull. Soc. pediat. de Paris **22:** 398, 1924.
947. PHILLIPS, J. McI.: J. A. M. A. **78:** 497, 1922.
948. MAXWELL, L. A. I.: M. J. Australia **2:** 483, 1923.
949. DE BESCHE, A.: Acta path. Scand. **6:** 115, 1929.

reported an instance due to gooseberry marmalade; Urbach[26] cases due to fish (Fig. 171), cauliflower, strawberries, milk, cheese, sardines (Fig. 172), and pork (Figs. 173, 174).

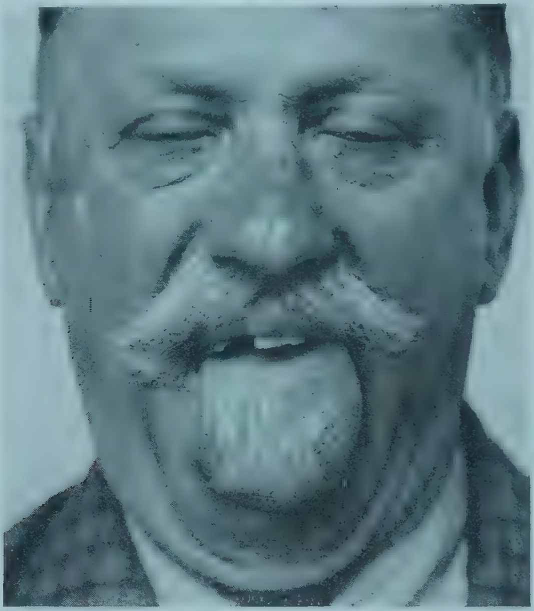

FIG. 172. ANGIONEUROTIC EDEMA OF TONGUE DUE TO ALLERGY TO SARDINES

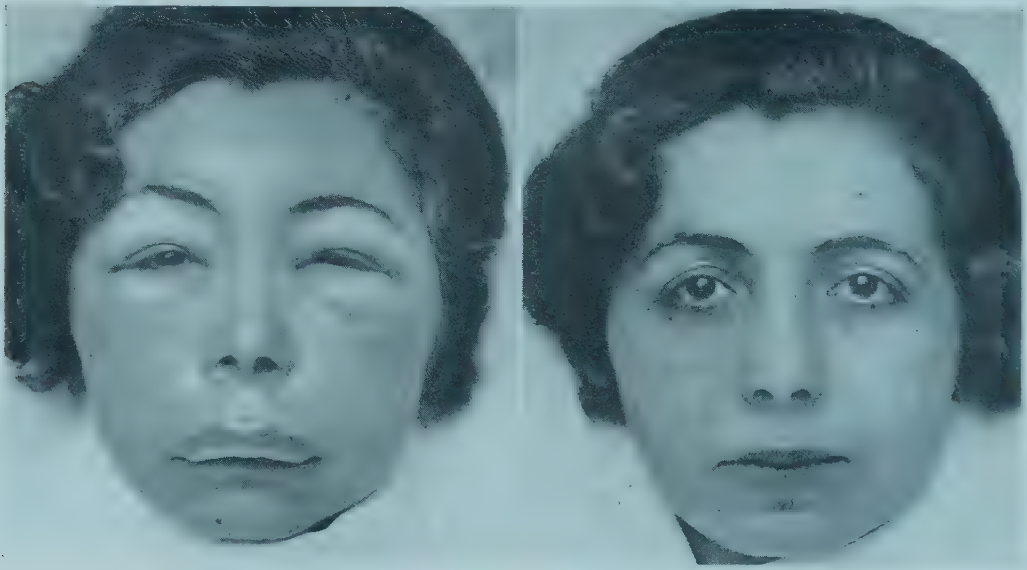

FIG. 173 FIG. 174

ANGIONEUROTIC EDEMA DUE TO HYPERSENSITIVENESS TO PORK

FIG. 173. Appearance before treatment.

FIG. 174. After two weeks' treatment with Pork Propeptan the patient could eat this food with impunity.

In some rare instances the edema has been found to be evoked by mere epidermal or mucosal contact with the allergen. Thus, Vaughan[588] reported a case of angioneurotic edema of the tongue and hands after eating watermelon, in which the same swelling of the hands appeared on mere contact with the juice of the watermelon.

Inhalant allergens are also capable of eliciting these swellings. Here it must be assumed that the causative substances are resorbed by the mucous membranes of the upper respiratory passages.

Angioneurotic edema has also been observed in animals. Both van Leeuwen[950] and Phillips[947] reported the condition in dogs, following ingestion of pork or fish. Schwyter described a case of fatal edema of the larynx in a cow.

C. LICHEN URTICATUS

Lichen urticatus is an entity characterized by the presence of numerous intensely pruritic, usually excoriated papules with central bloody crusts. They occur principally on the extensor surfaces of the upper extremities, with a marked tendency to spare the flexor aspects. In cases of long duration other areas may also be involved, particularly the buttocks and the extensor surfaces of the legs. In infants and small children lentil-sized, watery, clear vesicles are not infrequently observed; they are usually quite deep in the cutis and located on the soles of the feet.

The opinion has been expressed that lichen urticatus may be regarded as a variant of urticaria. We are strongly inclined to reject this view, however, because of the radical differences in the two clinical pictures. Moreover, we consider the argument that, to a certain extent, both have a common etiology, to be irrelevant in this connection.

Lichen urticatus can be caused exogenously and endogenously. It would be a gross error to suppose that all cases, especially in adults, are necessarily of allergic origin. The disease can, in fact, be brought on by a variety of conditions, such as gastrointestinal disturbances (enteritis, colitis, constipation), chronic cholangitis, kidney disease, ovarian dysfunction, and parasitic infestations. No deductions can be drawn from the clinical picture as to whether a given case is of allergic origin. It is necessary, therefore, to subject each patient not only to exhaustive internal examination, but also to allergic tests, including the environmental test, diet trials, Propeptan diet, and the like. Skin tests are of limited value and, in cases of nutritive allergy, almost invariably useless (Walzer and Grolnick[951]). The results of these studies will permit the physician to conclude whether the case is attributable to an underlying allergy.

For the sake of clarity, it may be best to discuss separately the manifestations of lichen urticatus in adults and in small children.

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[950] van Leeuwen, S.: München. med. Wchnschr. **78**: 529, 1931.

[951] Walzer, A. and Grolnick, M.: J. Allergy **5**: 240, 1934.

In adults lichen urticatus usually presents the typical picture of excoriated papules on the extensor aspects of the upper extremities and occasionally also on the back, buttocks, and legs. There are, moreover, atypical forms of the disease, a fact that does not seem to be sufficiently well known.

Fig. 175 shows a case which from the clinical point of view is very similar to prurigo Hebra except for the absence of lymphadenopathy, the so-called prurigo buboes. The duration of the illness in this woman was ten years. Nutritive allergens were found to be eggs, pork, carrots, pepper, paprika, and table salt, each having been established separately. The hypersensitiveness to eggs, pork and carrots was controlled by means of type-specific Propeptans, temporarily at first, and permanently later on. The condiments were omitted from the diet, and table salt was replaced by Curtasal (see p. 235). By these procedures a complete remission of the skin manifestations was obtained within four weeks without resorting to any local measures (Fig. 176). In other words, the patient was able to eat with impunity eggs, pork, and carrots without Propeptans, while condiments and salt regularly produced cutaneous symptoms.

As a further example we present Figure 177 which shows variola-like scars and brownish purple spots 0.5 cm. in diameter. The latter were partly oozing, and their perimeters showed the remains of blisters. These lesions were of many years' duration and were distributed over the scalp, neck, shoulders, breasts, upper arms, buttocks, and lateral surfaces of the thighs. This bullous form of lichen urticatus closely resembled pemphigus vulgaris. It was found to be due to hypersensitiveness to wheat and egg and was entirely healed within two months by means of Propeptan therapy.

In another case which the writer observed, the clinical picture resembled closely that of dermatitis herpitiformis Duhring (Fig. 178). A similar observation concerning the appearance of bullous skin lesions as a clinical expression of food allergy was reported by Gougerot and Blamoutier.[952] These authors demonstrated that their patient developed bullous eruptions after partaking of chocolate and champagne.

Facio[953] has described a condition, said to be very common in Argentina, which he calls "simple acute prurigo with circumscribed lichenification"; the condition is analogous to, if not identical with, what we call lichen urticatus. In the Argentine the disease is in many instances considered to be due to the fact that the shepherds habitually overindulge in alcohol when they go into town, and then also eat food to which they are not accustomed. The condition manifests itself first by diarrhea and fever, accompanied by intense itching which attains its maximum within about five or six days; then cutaneous lesions appear, consisting of numerous lichenified papules. After a few weeks the dermatosis begins

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952. Gougerot, H. and Blamoutier, P.: Arch. dermatosyph. hôp. St. Louis **2:** 318, 1930.
953. Facio, L.: Semana med. **2:** 172, 1930.

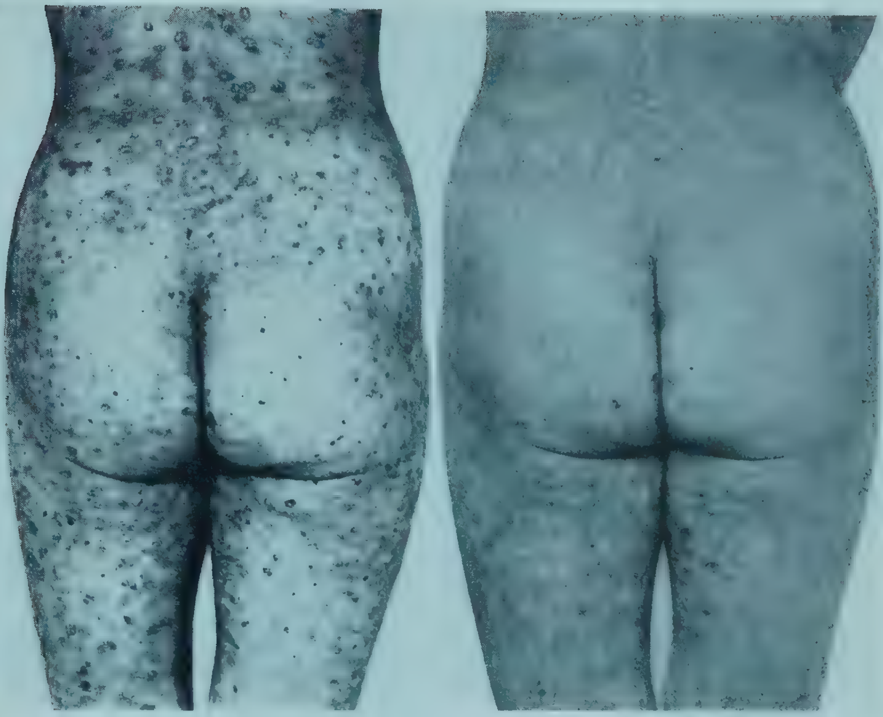

Fig. 175 Fig. 176

Lichen Urticatus of Many Years' Duration Due to Multiple Food Allergy (Pepper, Paprika, Salt, Carrots, Eggs, Pork)

Fig. 175. Appearance of skin before treatment.

Fig. 176. Healed, with pigmentation, after four weeks of Propeptan therapy, use of salt substitute, and elimination of spices.

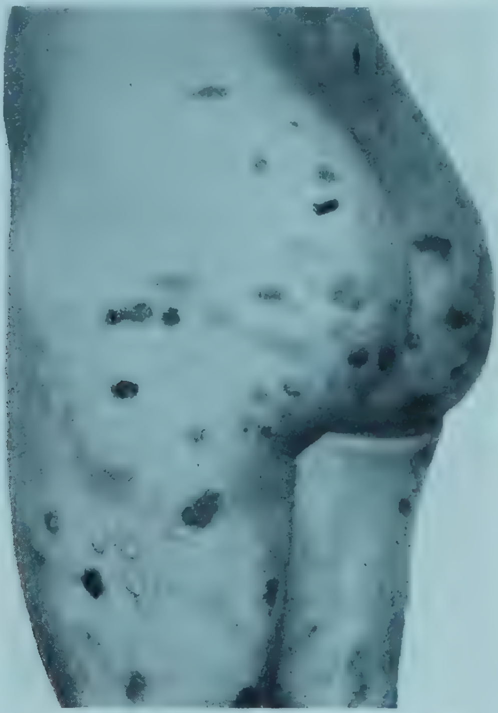

Fig. 177. Bullous Form of Lichen Urticatus of Ten Years' Duration, Clinically Resembling Pemphigus Vulgaris

Allergens proved to be egg, wheat, and pork. Cured by Propeptan therapy in eight weeks.

to regress, unless secondary cutaneous manifestations arise and prolong the course of the disease. This example affords an excellent illustration of nutritive allergization as a result of gastrointestinal irritation by overindulgence in alcohol, and might very well, *mutatis mutandis*, serve to explain the pathogenesis of the nutritive-allergic forms of lichen urticatus in many cases outside Argentina.

In seeking to identify the causative food allergen, it is to be borne in mind that not only animal and vegetable foods but also carbohydrates, fats, acids, and salts must be considered. It should also be remembered that not every case of allergic lichen urticatus is necessarily one of allergy to some food. For instance, some are due to bacterial allergy arising from dental or tonsillar infection or from pyelitis. Furthermore, the author[26] observed a number of cases in which exogenous-allergic factors were involved. Appropriate diagnostic methods usually revealed the identity of the allergen.

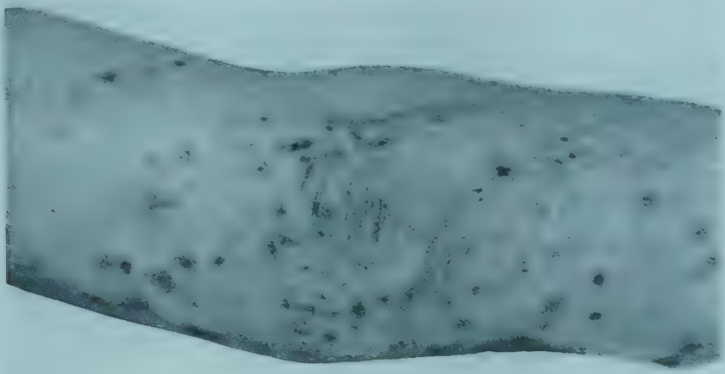

FIG. 178. LICHEN URTICATUS CLINICALLY RESEMBLING DERMATITIS HERPETIFORMIS OF DUHRING

Lichen urticatus in infants and small children is a relatively common disease (Figs. 179, 180, 181, 182). Occasionally the first eruptions make their appearance when the child is being weaned and placed on artificial feedings; more commonly, however, the condition is associated with some gastrointestinal disease or digestive disturbance. This pathogenesis serves to explain why the condition is almost invariably of nutritive-allergic origin in infants and why it can be often cured rapidly by proper dietetic measures or by administration of Propeptans. The same holds true, but to a much lesser extent, in the case of small children.

In the majority of children, lichen urticatus is fully cured spontaneously after running a course lasting from months to one or two years, and characterized by prolonged symptom-free intervals which become progressively lengthened. In some cases, however, the recurring attacks increase in severity and the condition finally assumes the characteristic picture of Hebra's prurigo, consisting of only slightly elevated, intensely pruritic papules, with secondary lichenification and hyperpigmentation of the skin, accompanied by the appearance of so-called prurigo buboes.

The writer[954] had occasion to study 225 cases of lichen urticatus in children of all ages. In all instances in infants and very young children an underlying nutritive allergy was demonstrable. In older children actual elicitation of an attack by administration of a given food (usually milk, egg, veal, or pork) was regularly possible in only 30 cases; and in these same children, withdrawal of those food items prevented the appearance of symptoms. In additional cases it was found that not one but several foods in combination constituted the causative agents, as follows: milk and egg; smoked meat and spinach; potato and apple; egg and apple. In one child the symptoms could be evoked only by giving a soup composed of tomatoes, lemons, and bouillon cubes; the individual ingredients ingested separately elicited no response. Administration of Polypropeptans re-

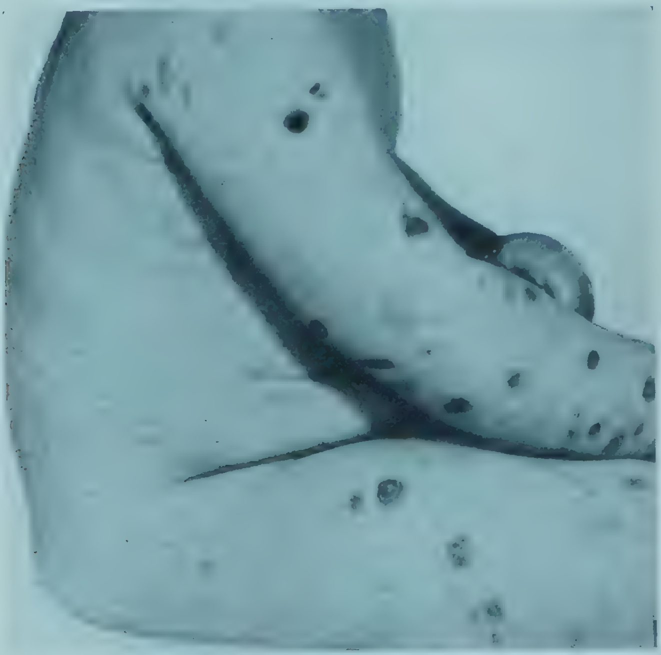

FIG. 179. TYPICAL DISTRIBUTION OF LICHEN URTICATUS IN CHILDREN

Note the involvement of the extensor surfaces of the extremities.

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[954] URBACH, E.: Dermat. Ztschr. 78: 77, 1938.

sulted in a complete cure in 15 cases, although it was impossible to identify the nutritive allergens. According to Bray,[955] pork products, fish, eggs, potatoes, chocolate, and particularly fats are usually the exciting factors.

In children past the age of 3, it was found that exogenous factors played a dominant part in the etiology. It is true that animal and vegetable foods as well as carbohydrates (Weigert,[622] Mathieu,[956] Urbach[954]) are operative in a small percentage of cases; but in the great majority, environmental tests, as well as skin tests, will reveal some allergen in the patients' surroundings as the causative agent. Lastly, one must not

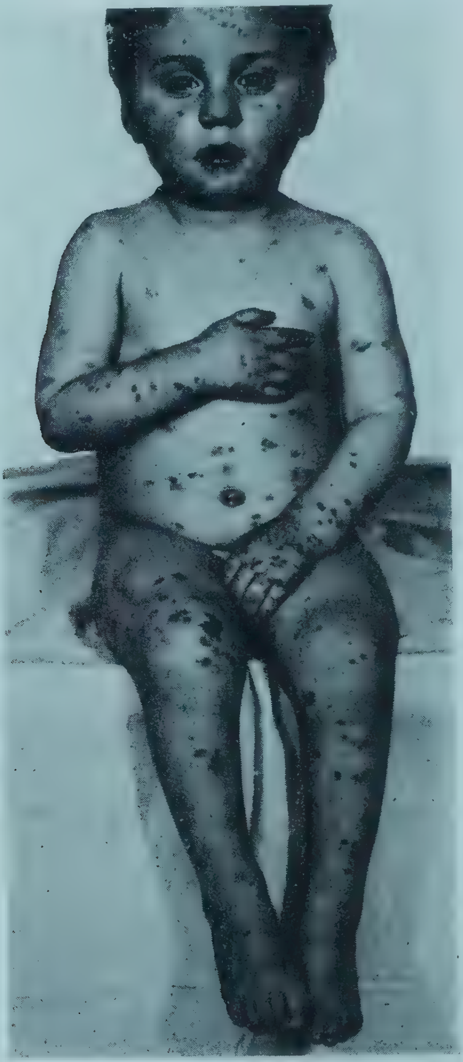

Fig. 180. Generalized Lichen Urticatus Due to Milk Allergy

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955. Bray, G. W.: Brit. J. Child. Dis. **30:** 180, 1933.
956. Mathieu, R.: Bull. Soc. de pédiat. de Paris **26:** 519, 1928.

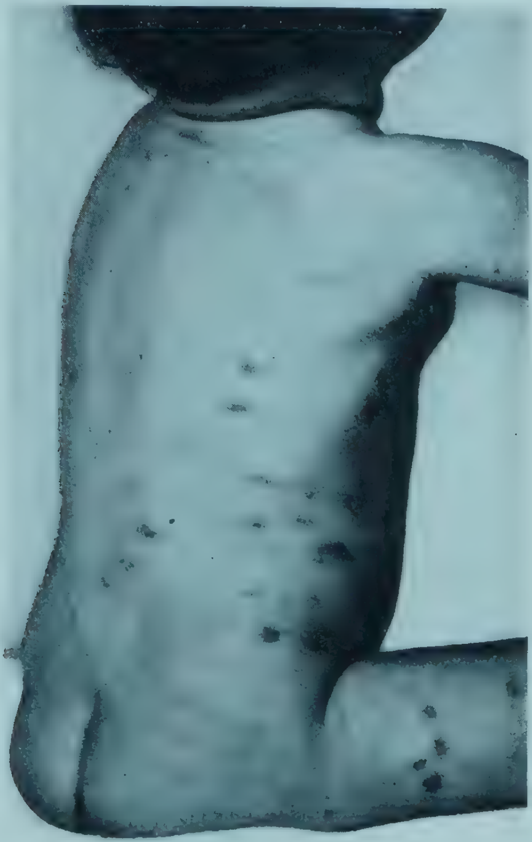

FIG. 181. LICHEN URTICATUS DUE TO WHEAT HYPERSENSITIVENESS

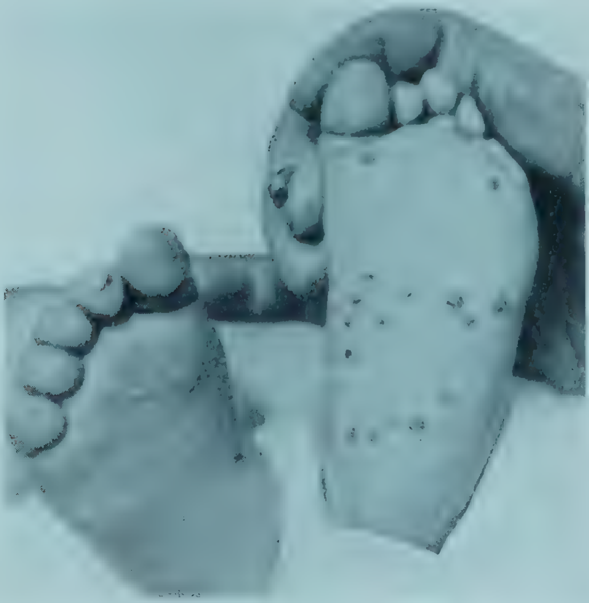

FIG. 182. BULLOUS LICHEN URTICATUS DUE TO SPINACH HYPERSENSITIVENESS

fail to consider the possibility of endogenous allergens of a bacterial nature (resulting from tonsillitis, otitis, respiratory infections) and parasitic infestations. Nor should the fact be overlooked that fever, gastrointestinal disturbances, and the like can provoke recurrences of lichen urticatus after a long period of freedom from symptoms.

As stressed above, lichen urticatus is by no means necessarily of allergic origin. According to Pillsbury and Sternberg,[957] the condition may sometimes be related to a calcium deficiency as a result of precipitation of absorbable calcium by oxalates in the foods. Such cases may be cured by parathyroid hormone therapy. In other instances external causes, such as insect bites (especially flea and bedbug), have been identified as the cause.

The therapy consists entirely of the discovery and elimination of the causal agent; when the condition is found to be due to some nutritive allergen, the therapeutic measures outlined on page 256 are to be instituted.

D. PRURIGO

In connection with the discussion of lichen urticatus, the relatively uncommon but nonetheless important entity known as prurigo merits consideration. Distinction is made between two forms of the disease, which differ only in degree: a severe type, prurigo ferox of Hebra, and a comparatively mild type, prurigo mitis.

Clinically the disease is characterized by the sudden appearance of pinhead- to lentil-sized colored papules. From the onset of the condition the patient suffers from extraordinarily intense itching, which may be constant or in the form of recurring attacks. The parts most likely to be affected are the extremities, the upper more commonly than the lower. As a result of the uncontrollable scratching, the skin becomes thickened; at the same time the lymph nodes undergo a characteristic indolent swelling leading to the so-called prurigo buboes in the inguinal, epitrochlear, and axillary regions.

The pathogenesis of this disease is not uniform. J. Jadassohn called attention to the importance of environmental factors. It is an old clinical observation that a few days' hospitalization, without any treatment whatsoever, will frequently render a patient with prurigo symptom-free, even the prurigo buboes disappearing spontaneously. Moreover, it has been commonly observed that shortly after the patient's discharge, usually within a few days, but sometimes on the very night of his return home, the subjective or objective cutaneous manifestations recur.

It should be noted, however, that the search for the excitant should by no means be limited to contactant and inhalant factors. Thus, the writer observed a girl of 10 years whose prurigo was found to be due to an extreme hypersensitiveness to milk (Fig. 183). Propeptan treatment over a period of three weeks cured the condition. Moreover, not only protein foods, but also salts, acids, spices, and the like must be considered as potential allergens, and appropriate diet trials should be instituted. Treatment will therefore depend on discovering the underlying etiologic factors.

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[957] Pillsbury, D. M. and Sternberg, T. H.: Am. J. Dis. Child. 53: 1209, 1937.

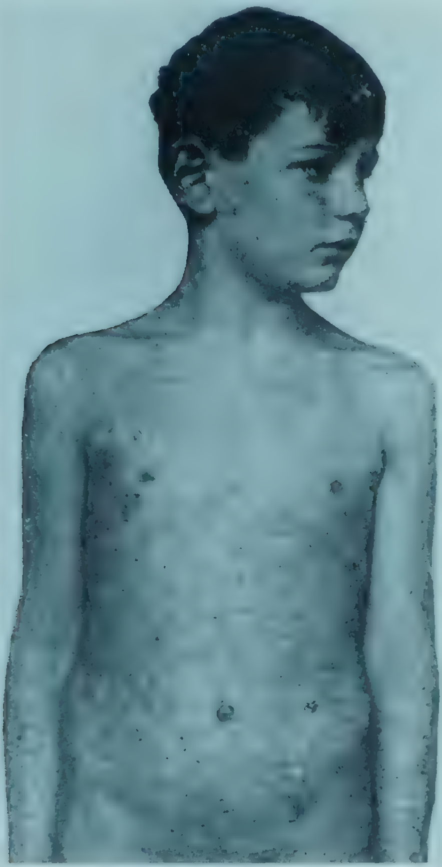

Fig. 183. Prurigo Ferox of Hebra on the Basis of Allergy to Milk

E. PRURITUS

Itching, local or generalized, is probably the commonest as well as the most distressing of all phenomena encountered in dermatology. Needless to say, we refer not to the forms of itching manifestly due to local inflammation or other local cutaneous disease, but rather to those not uncommon cases in which the itching improves only following discovery and treatment of some underlying gastrointestinal, hepatic, gallbladder, or renal disease, or of a metabolic or nutritional disorder.

In occasional cases the pruritus is unquestionably of allergic origin (Fig. 184). Here, elimination and re-exposure tests constitute the only means by which the diagnosis can properly be made; that is, if the pruritus ceases promptly on avoidance of the suspected agent (food, drug) and reappears following deliberate re-exposure to it, the condition is an expression of an allergic hypersensitiveness to the given agent. Cohen[958] described two cases in which generalized pruritus was the only symptom of a nutritive allergy (one to pork, the other to buckwheat and potatoes).

The question as to whether pruritus following the use of coffee, tea, and alcohol is to be regarded as an allergic manifestation or as an expression of irritability of the central or peripheral nervous system, resulting in dilatation of the cutaneous blood vessels, must be decided in each case by appropriate tests. Rothman[959] feels that the pathogenetic role of the central nervous system is strongly indicated by the fact that individuals presenting other signs of heightened irritability of this system are precisely the ones to complain of itching following the use of coffee or tea. Implication of the peripheral vasodilator system seems most unlikely in view of the fact that, so far as we know, the literature contains no report of congestive reddening of the skin after drinking coffee or tea. On the other hand, the pruritic effect of alcohol might well be due to temporary

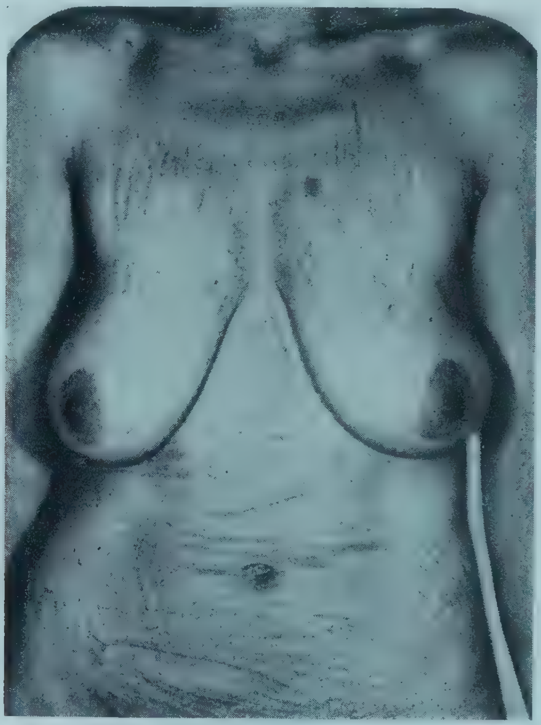

FIG. 184. PRURITUS DUE TO HYPERSENSITIVENESS TO PORK

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958. COHEN, M. B.: J. A. M. A. 76: 377, 1921.
959. ROTHMANN, S.: Handb. d. Haut- u. Geschlechtskr. 6: 1, 1927 ed. by J. Jadassohn.

irritability of both the central and the peripheral nervous systems, the latter as a result of dilation of the blood vessels of the skin. We are inclined to attach considerable importance to observations reported by Bulkley, S. Jessner, Huebner, and others that stimulants not uncommonly constitute the cause of pruritus ani and pruritus vulvae.

However, pruritus ani and pruritus vulvae (Fig. 185) are generally a symptom and not a disease entity. First of all, the various metabolic diseases, notably diabetes mellitus, may be the cause of pruritus. The writer strongly recommends performance of a sugar tolerance test in every case of refractory pruritus of unknown origin. Should it be impossible to perform this test, for one reason or another, diabetic diet should be tried and even insulin therapy for a week or so. The writer recommends this procedure because blood sugar tolerance tests sometimes prove to be unreliable and skin sugar investigations are not readily carried out in everyday practice.

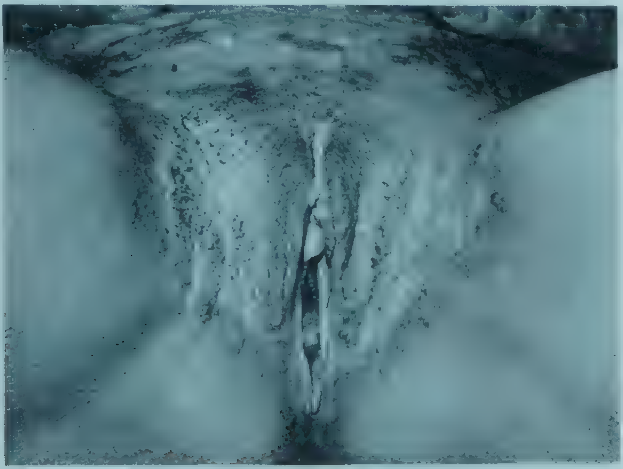

FIG. 185. PRURITUS VULVAE ON A DIABETIC BASIS

The pruritus was the first symptom of diabetes. Fasting blood sugar level, 380 mg. per cent.

There can be no doubt that itching is occasionally caused by gout and can be combated etiologically by the appropriate dietary therapy plus neocinchophen and colchicine. However, we wish to counsel against the tendency of some authors to regard every case of generalized pruritus as of gouty origin. For detailed discussion of this point see page 106. On the other hand, in instances of true gout this etiology should be considered. Thus, Schamberg and Brown[875] have achieved cures with a purine-free diet in pruritus presenting abnormally high blood uric acid levels.

Itching caused by foods need not always come as a direct consequence; on the contrary, foods very frequently constitute the indirect cause of pruritus by giving rise to gastrointestinal disorders which, in turn, lead to the absorption of improperly digested protein substances, and thus, among other things, to the production of dermatoses often marked by pruritus alone in their initial stages. Voluminous indeed is the literature on the role of gastric secretory anomalies and motor disturbances, of diseases of the duodenum, of other segments of the small intestine, of the large intestine, liver, and of gastrointestinal intoxications in the production of pruritus and its cure following eradication of the underlying disturbance. For a discussion of the dietary therapy for cases of this kind, the reader is referred to Chapter III.

Moreover, the importance of constipation warrants special emphasis, as does the need for treating this condition by means of dietary therapy. In our experience colonic irrigation has proved to be an excellent method of determining quickly whether constipation is actually the cause of the pruritus. Furthermore, it is interesting to note Swift's allegation,[960] that pruritus vulvae is occasionally associated with achlorhydric anemia in patients with achylia gastrica, and responds to liver therapy plus dilute hydrochloric acid.

Pruritus is not uncommonly seen in connection with chronic nephritis. In cases of this kind, relief from itching depends on treatment of the renal disease.

Lastly, the importance of psychic factors cannot be overemphasized. While in some cases the itching is merely an expression of emotional imbalance, in othes it is due to psychosomatic influences, especially during the menopause.

In cases of pruritus ani one should always look for intestinal fermentation, which often causes considerable increase in secretion, thereby intensifying the itching. Dietary therapy, as outlined on page 322, will correct this situation. On the other hand, in cases in which the reaction of the stool is found to be alkaline, Aitken[940] recommends one pint of buttermilk and one tablespoon of lactic oats daily for two or three months. Moreover, it is well to bear in mind that this condition is sometimes associated with gallbladder disease, obstruction of the portal circulation, and other conditions causing distention of the hemorrhoidal veins. Constipation and straining at stool may also act as a factor in obstructing the venous return flow. Local pathologic lesions of the anus, such as fistulas, fissures, infected anal ulcers, cryptitis, and ulcerated hemorrhoids with slough should be eliminated by surgery. Lastly, a simple, well balanced diet should be prescribed. Overindulgence in highly seasoned, rich, heavy foods, which is all too common, is likely to exert an unfavorable influence on the intestinal flora. Elimination of these foods from the diet often serves to bring the pruritus under control promptly.

[960] Swift, B. H.: M. J. Australia 2: 541, 1932.

One occasionally encounters a case of pruritus ani (Fig. 186) or of pruritus vulvae which proves to be of allergic origin. Instances of this kind have been reported by Wynn,[961] Rowe,[962] Vaughn,[963] Andreson,[964] Drueck,[965] Tuft,[966] Stokes,[967] and others.

In view of the fact that pruritus can be due to a great variety of causes, it is naturally impossible to recommend a general therapeutic approach. Each case must be subjected to painstaking internal investigation with the object of determining, first, whether there is any evidence of metabolic imbalance, hematopoietic disease, gastrointestinal disorder, endocrine dysfunction, focal infection, parasitic infestation, or, above all, of a disturbing psychic influence, any one of which might be the fundamental cause. If none of these conditions is found, the next thing to be done, especially in cases with personal or family histories of allergy, is to con-

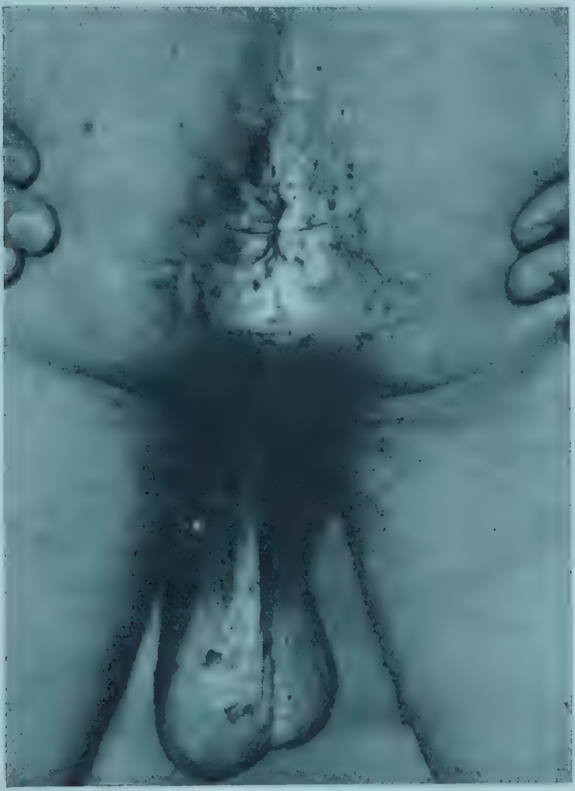

FIG. 186. PRURITUS ANI DUE TO HYPERSENSITIVENESS TO MILK
Dermatitis appeared only after many years of pruritus

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961. WYNN, J.: J. Lab. & Clin. Med. **13:** 16, 1927.
962. ROWE, A. H.: J. A. M. A. **91:** 1623, 1928.
963. VAUGHAN, W. T.: South. M. J. **56:** 725, 1930.
964. ANDRESON, A. F. R.: Med. J. & Rec. **122:** 271, 1925.
965. DRUECK, C. J.: Urol. & Cutan. Rev. **39:** 490, 1935.
966. TUFT, L.: Clinical Allergy. Philadelphia: Saunders, 1937.
967. STOKES, J. H.: Internat. Clin. **1:** 147, 1940.

sider the possibility of an allergic hypersensitiveness. This may involve all types of studies, including elimination, environmental, and possibly also skin tests, as well as tests for physical allergy, all designed to determine the exact nature of the hypersensitiveness, if any. When none of these investigations clarifies the pathogenesis, it is necessary to resort to nonspecific therapeutic methods, the most promising of which is roentgen irradiation. In dealing with senile pruritus, the writer has repeatedly found the treatment originally introduced by Luithlen[968] to be helpful. This investigator showed that a high silicic acid diet (drinking an infusion of the herb horsetail, *equisetum arvense*) leads to marked improvement. However, we have found that even better results can be obtained by intravenous injections of a 1 per cent solution of sodium silicate (a course of fifteen injections, beginning with 1 cc. daily, then 2 cc. daily). Von Noorden and Salomon[319] have observed occasional cases of senile pruritus in which a salt-poor diet was definitely beneficial.

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968. Luithlen, F.: Wien. med. Wchnschr. 73: 614, 1923.

CHAPTER X

Psoriasis

All the studies performed on patients with psoriasis vulgaris have, to date, failed to disclose any metabolic disturbance as the underlying cause of this dermatotis. In spite of this fact, efforts to treat this disease dietetically continue unceasingly, with reports claiming excellent results, from which are drawn conclusions, mostly unsubstantiated, as to the etiology of psoriasis. These will be critically evaluated in the following pages.

More than thirty-five years ago, Bulkley[969] and Brocq[274] stressed the role of overfeeding in the pathogenesis of psoriasis. This conforms perfectly with the well known fact that in World War I, under the influence of the quantitatively and qualitatively inferior diets prevalent in Germany and Austria, many psoriatic individuals, particularly those who had previously been overfed, experienced a complete remission of their disease, which reappeared, however, in the postwar period. Nathan and Stern,[175] by instituting repeated fasting periods of from eight to ten days each, achieved considerable improvement in two cases of erythrodermatic psoriasis which had resisted all manner of therapy for many years. Wright[970] reports the spontaneous cure of a patient with widespread psoriasis following a severe attack of dysentery. Cornbleet[255] believes that weight-reducing diets are helpful. He therefore limits the intake to 1,200 to 1,500 calories daily, depending on weight, sex, and amount of physical work done. The desire for food is curbed by administering appropriate amounts of amphetamine sulfate. Many years ago the present writer[254] demonstrated that although a prescribed diet is free from fat or low in protein it is therapeutically ineffectual in psoriasis if it is otherwise adequate in calories.

Over thirty-five years ago Brocq[274] claimed that strict adherence to a vegetarian diet has a curative influence in many patients with extremely refractory psoriasis, and he stressed the superiority of the dietary approach over local measures. Bulkley[969] reported cases that were free from recurrences for months and even years on a strict meat-free diet. But Schamberg[265, 266] was the outstanding protagonist of the low protein diet. Together with his collaborators he demonstrated, in extensive studies of protein metabolism, that psoriatic individuals give definite signs of abnormal nitrogen retention. On the basis of these findings, he placed his

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969. Bulkley, L. D.: J. A. M. A. 59: 535, 1912.

970. Wright, C. S.: Nutrition and Diseases of the Skin: in Dietotherapy, ed. by Wohl, M. G. Philadelphia: Saunders, 1945.

patients on a diet containing no more than 4 or 5 Gm. of nitrogen, on which the patients' weight remained virtually constant. Without going so far as to say that food is the cause of psoriasis, Schamberg stated that, in his experience, a low nitrogen diet (see Table 31 on p. 105) without any other treatment, external or internal, caused the lesions of psoriasis to disappear, partially or completely (Figs. 187, 188); and, furthermore, that this kind of dietary brings the psoriasis lesions into such a state of quiescence that the skin tolerates local medication which could not be applied previously. The possible explanation of the efficacy of his dietary regimen is more fully discussed on page 102.

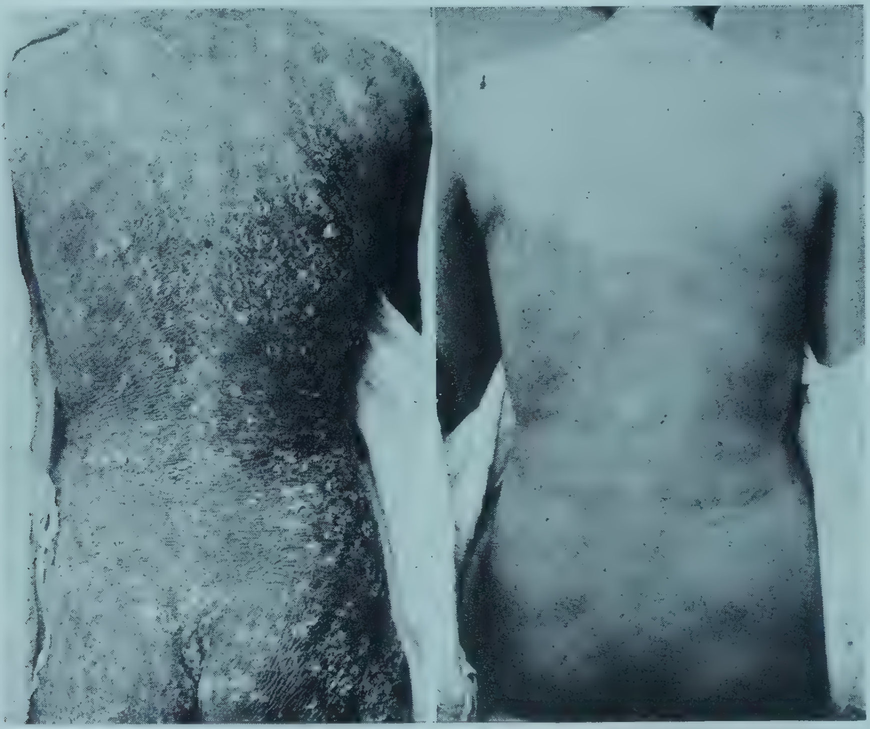

FIG. 187 FIG. 188

INFLUENCE OF LOW PROTEIN DIET ON PSORIASIS

FIG. 187. Appearance of lesions before institution of diet.

FIG. 188. After three months on a low protein diet, with no other internal therapy or local treatment except the occasional use of vaseline.

A number of authors who tried Schamberg's low protein diet in very severe cases reported excellent results (Becker and Obermayer,[269] Bloch,[971] Brundage,[270] Schiff,[271] Stokes,[272] Strickler[273]). Particularly interesting is a report by Wright,[970] a close collaborator with Schamberg, of thirty-six psoriasis patients whom he treated in a hospital with this diet. While they were all virtually free of lesions by the end of three or four weeks (in addition, local therapy was used), he stresses the lack of permanence in the results. The symptom-free periods ranged from eight months to twelve years. Many authors, however, including Unna, Pusey, Zon, and Urbach, have failed to note satisfactory improvement. This may be due to the fact that the patients of these latter authors were ambulatory during the dietotherapy and that consequently the nitrogen intake could not be strictly controlled, as postulated by Schamberg.

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[971] BLOCH, B.: Med. Klin. 6: 1527, 1910.

Gruetz and Buerger[972, 973] introduced a new concept by regarding psoriasis as an expression of a disturbance in fat metabolism, basing their views on the high lipid levels in the serum and the cutaneous lesions of patients with psoriasis, on the results of cholesterol tolerance tests (oral administration of 5 Gm. of cholesterol in 100 Gm. of olive oil), and on the favorable response to prolonged adherence to a diet low in fat. They interpret the clinical and histologic phenomena of psoriasis as an inflammatory reaction to a pathologic excess of lipoids in the blood, which is excreted by way of the cutaneous capillaries, causing the lesions of psoriasis. They state that when all food items containing fat and cholesterol are excluded, and the fat intake is limited to 20 Gm. daily for adults and 10 Gm. daily for children (see Table 28, on p. 99), clinical improvement in children will be noticed in three weeks, in adults in from six to eight weeks. The lesions will disappear completely within three to eight months, depending on the severity of the case. Occasionally, some of the older patches actually show signs of exacerbation at first, despite the diet, and a few new lesions make their appearance, simulating a general worsening of the condition. But, when the diet is systematically observed, the above-mentioned results are ultimately achieved.

However, psoriatic manifestations are likely to recur when the low fat regimen is replaced by a normal diet. The disadvantage inherent in both the low fat and the low protein diets is that they must be continued for a long time, and that they can be properly carried out only when adequate means and facilities are available. It is advisable, therefore, to prescribe the low fat diet only in very severe cases, in which the patients suffer so much that they are willing to endure all of the inconveniences and discomforts of the regimen.

The effects of the low fat diet have been extensively studied. Madden,[974] Semon,[975] Incedayi and Ottenstein[976] have reported very good results. However, Marchionini[149] noted improvement only in acute

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972. Gruetz, O. and Buerger, M.: Klin. Wchnschr. **12**: 373, 1933.
973. Gruetz, O.: Arch. f. Dermat. u. Syph. **177**: 246, 1938.
974. Madden, J. F.: Arch. Dermat. & Syph. **39**: 268, 1939.
975. Semon, H. C.: Proc. Roy. Soc. Med. **28**: 507, 1935.
976. Incedayi, K. and Ottenstein, B.: Acta dermato-venereol. **21**: 674, 1940.

exudative and in erythrodermatic forms of psoriasis. Neither Dodds and associates[977] nor Wise and Sulzberger[978] were especially impressed by the results of a reduction in the fat intake; however, the reported lack of response to the low fat diet may well be due to the difficulties encountered in maintaining the diet for ambulatory patients.

While the writer readily agrees that the clinical results of a low fat diet are often very satisfactory[254] (Figs. 189, 190), he concurs with Schaaf and Obtulowicz,[979] Madden,[974] Herring,[980] and others in denying the validity of the concept that psoriasis is a lipoid disease. In the first place, hypercholesterolemia is not, as a rule, associated with psoriasis (LeWinn and Zugerman,[253] Madden,[252] Rosen et al.[981]). Moreover, the cholesterol tolerance test cannot be considered as a reliable index of lipid metabolism (Madden[252]). The work of LeWinn and Zugerman[253] indicates that psoriasis patients show no significant aberration from the normal in regard to the ability to metabolize fats, as judged by the rate of their disappearance

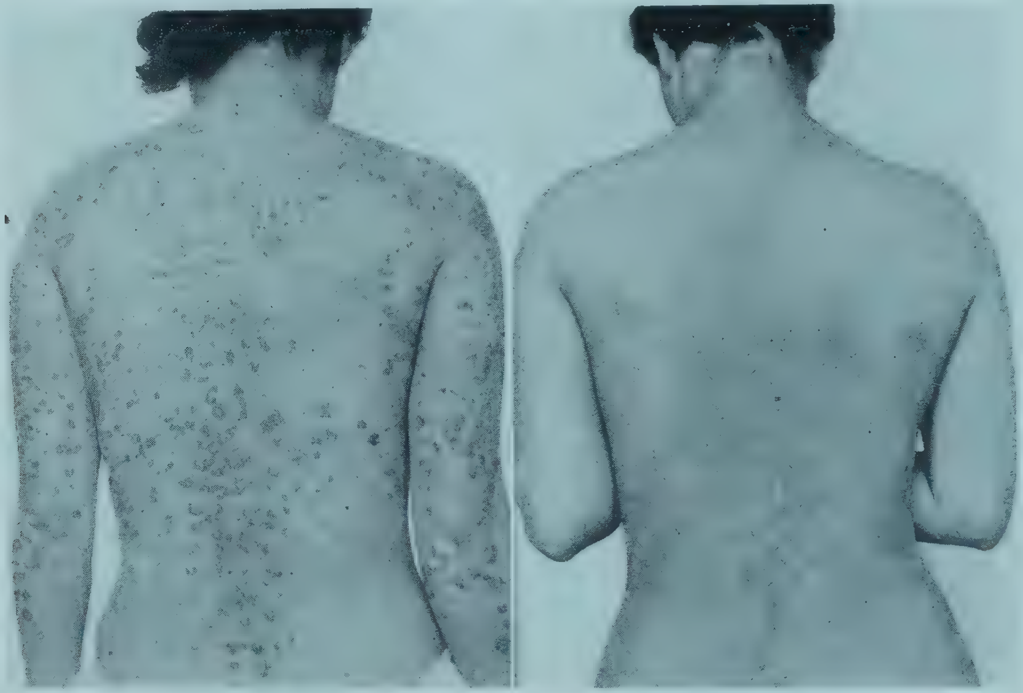

Fig. 189 Fig. 190

Influence of Low Fat Diet on Psoriasis

Fig. 189. Before treatment.
Fig. 190. After eight weeks of low fat diet.

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977. Dodds, E. C., MacCormac, H., and Robertson, J. D.: Brit. J. Dermat. **54:** 212, 1942.
978. Wise, F. and Sulzerger, M. B.: 1942 Year Book of Dermatology and Syphilology. Chicago: Year Book Publishers, 1943.
979. Schaaf, F. and Obtulowicz, M.: Arch. f. Dermat. u. Syph. **173:** 200, 1935.
980. Hering, H.: Dermat. Wchnschr. **106:** 80, 1938.
981. Rosen, I., Rosenfeld, H. and Krasnow, F.: Arch. Dermat. & Syph. **35:** 1093. 1937.

from the blood stream, the total cholesterol of whole blood being used as the criterion. Lastly, Burks and Montgomery[982] studied the fat content of psoriatic lesions in twenty-five cases and found no increase in the lipids of the skin.

Madden[252] explains the favorable effect of the low fat diet on the basis of a general readjustment of metabolism, and of tissue function, rather than on the basis of the correction of an underlying disturbance of the fat metabolism.

In recent years work has been done along other lines in an attempt to prove that psoriasis is an expression of a disturbance of lipid metabolism. The lipotropic factor is now generally assumed to be a substance which prevents or removes an accumulation of excess fat in the liver. According to McHenry and Patterson,[983] the lipotropic factor applies to three groups of substances: (1) insulin-free pancreatic extracts, called lipocaic, (2) choline, choline precursors, and related compounds, and (3) inositol. Walsh, Clark, Dragstedt, and Becker[984] have reported that lipocaic administered orally rendered 31 per cent of their patients symptom-free, while 50 per cent of the total number treated showed appreciable improvement. Gross and Kesten[124] achieved gratifying results in a series of psoriasis patients with lipotropic substances derived from foodstuffs such as soy bean lecithin and defatted wheat germ, which contain, respectively, choline and inositol, and choline and biotin. These lipotropic substances were also effective in reducing an elevated serum cholesterol level. The average daily dose of soy bean lecithin varied between 30 to 60 Gm. With the disappearance of the lesions the patients were kept on a maintenance dose of 4 to 8 Gm. daily. Defatted wheat germ was given in doses of 30 to 45 Gm. a day, and the maintenance dose was 15 to 40 Gm. daily.

According to Gross and Kesten,[124] the favorable response of psoriasis to lipotropic substances derived from foodstuffs reflects, not a nutritional deficiency, but rather an increased need for certain substances essential to the synthesis of enzymes involved in lipid metabolism. Goldman[985] also obtained good results with soy bean lecithin. He reports, however, that relapses occurred when the lecithin was discontinued, and that it was difficult to produce similar improvement when the lipotropic substance was resumed. The present writer was not impressed with the response to this form of therapy for psoriasis.

The question as to whether psoriasis is somehow connected with dia-

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982. Burks, J. W. and Montgomery, H.: Arch. Dermat. & Syph. **48**: 479, 1943.
983. McHenry, E. W. and Patterson, J. M.: Physiol. Rev. **24**: 128, 1944.
984. Walsh, E. N., Clark, D. E., Dragstedt, L. R. and Becker, S. W.: J. Invest. Dermat. **4**: 59, 1941.
985. Goldman, L.: Cincinnati J. Med. **23**: 166,1942.

betes mellitus or with other disturbances of carbohydrate metabolism is likewise a highly controversial one. The assumption that there is a causal correlation between the two was given a new lease on life by clinical observations pointing to a strikingly high incidence of psoriasis in occasional diabetic families. Furthermore, this assumption received considerable support from reports on the frequency with which elevated blood sugar levels (Pułay[986]) and, above all, pathologic glucose tolerance test curves were encountered among psoriatics, (Incedayi and Ottenstein,[987] Rost[987a], Moncorps and Speierer[987b]). Although it is true that psoriasis patients occasionally exhibit a moderate elevation of the blood sugar levels in the tolerance test, it has been clearly demonstrated, notably by the extensive series of investigations carried out by Koenigstein and co-workers,[988] that the incidence of diabetes among psoriasis patients is no greater than that among the population as a whole. This conforms perfectly with the writer's own blood and skin sugar tests on fairly extensive psoriasis material. Moreover, in contrast to Lortat-Jacob's findings,[989] the writer has never noticed any response on the part of psoriasis lesions to insulin medication—not even in cases in which the blood sugar curve was pathologically elevated or prolonged. In short, we are inclined to believe that if there is a relationship between diabetes and psoriasis, it is not that of cause and effect, but rather that both diseases are concurrent expressions of a common but as yet unidentified underlying mechanism.

From various quarters there have come reports of the beneficial influence of a salt-free diet. Thus, Gerson[198] claims to have achieved marked improvement with his diet; Doerffel[71] also reports gratifying results in exudative forms of psoriasis, and Loehe[990] noted considerable improvement in a case of psoriasis pustulosa universalis within seven weeks. On the other hand, according to Stuempke and Mohrmann,[991] 12 out of 22 patients showed no response whatever, 10 showed vague signs of a change in the condition, and the remaining 2 were the only ones to derive a beneficial effect from the diet. Sellei and Keining and Hopf reported a similar low percentage of results (only 3 out of 25 cases responding), and the present writer has never seen a single instance of definite improvement on a salt-free diet.

Incedayi and Ottenstein[290] reported encouraging results with treatment consisting of a low potassium diet plus ascorbic acid, designed to modify the action of the adrenal cortex, which, according to Grueneberg,[291] is insufficient in psoriasis. Together with LeWinn,[292] we treated a group of eighteen cases with a low potassium diet, vitamin C, and adrenal cortical extract, but failed to observe any definite benefit from this form of therapy.

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[986] Pulay, E.: Deutsche med. Wchnschr. **55:** 1175, 1929.

[987] Incedayi, K. and Ottenstein, B.: Dermatologica **80:** 18, 1939.

[987a] Rost, G. A.: Brit. J. Dermat. **44:** 57, 1932.

[987b] Moncorps, C. and Speierer, C.: Arch. F. Dermat. u. Syph. **164:** 642, 1932.

[988] Koenigstein, G., Goldberg, H., and Rappaport, D.: Wien. klin. Wchnschr. **43:** 125, 1930.

[989] Lortat-Jacob, L., Legrain, P. and Pellissier: Bull. Soc. franc. de dermat. et syph. **33:** 101, 1926.

[990] Loehe: Zentralbl. f. Haut- u. Geschlechtskr. **32:** 544, 1930.

[991] Stuempke, G. and Mohrmann, B. H. V.: Med. Klin. **27:** 235, 1931.

Strickler and Adams[99] as well as Grueneberg,[291] reported a high percentage of sulfur in psoriasis scales. Klauder and Brown[95] found high sulfur levels in the psoriasis skin, which showed a definite tendency to fall after the lesions had cleared. These authors felt, therefore, that the therapy of psoriasis should be directed toward reducing the high percentage of sulfur and that a low protein diet should be beneficial for this purpose. In interpreting the high percentage of sulfur in the skin of psoriasis patients, Klauder points to the fact that sulfur compounds, particularly glutathione, are essential physiologic tissue constituents concerned in biologic oxidation-reduction processes. There is evidence that the pathogenesis of psoriasis is in some way linked with the oxidation-reduction mechanisms of the epithelial cells, a view championed notably by van Kerckhoff.[992] In this connection, it is interesting to note the relationship between decreased urinary excretion of sulfur and of ascorbic acid in psoriasis patients (Reiss[993]). However, since there is no conclusive evidence that vitamin C therapy and, therefore, increased excretion of sulfur have a curative effect in psoriasis, there is some room for doubt that a disturbance of sulfur metabolism is directly concerned in the etiology of psoriasis.

In conclusion, we shall briefly consider the most modern approach of all, namely, vitamin therapy. Lutz[994] reported definite, although only temporary, improvement following administration of vitamin C in large doses. Similarly good results have been reported by Volpe,[995] Reiss,[993] Madden,[996] and Goldfarb.[997] But LeWinn and Urbach[292] and others have failed to note any distinct amelioration. While it is true that ascorbic acid excretion by psoriatics is below normal, Reiss[993] explains this on the basis that the cellular metabolism in the epidermis of psoriasis requires an unusually great supply of vitamin C, since the formation of scales tends to increase the utilization of the vitamin.

Goldfarb[998] reported improvement of psoriasis lesions following administration of vitamin P (267 mg. of eriodictin daily). This vitamin was chosen because of the relationship between mild injury and psoriasis on

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992. van Kerckhoff, J. H. P.: Beitrage zur Kenntnis der Psoriasis vulgaris. Leipzig: Hirzel, 1929.
993. Reiss, F.: Chinese M. J. **53:** 141, 1938.
994. Lutz, W.: Schweiz. med. Wchnschr. **65:** 1169, 1935.
995. Volpe: Med. Klin. **34:** 193, 1938.
996. Madden, J. F.: J. A. M. A. **115:** 588, 1940.
997. Goldfarb, A. E.: Arch. Dermat. & Syph. **43:** 536, 1941.
998. Goldfarb, A. E.: New York State J. Med. **44:** 1111, 1944.

the one hand and mild injury to the skin and increased capillary permeability on the other. Vitamin P has the capacity to restore pathologically heightened capillary permeability.

Large doses of vitamin D (300,000 units daily) were found very helpful by Ceder and Zon,[524] Brunsting,[525] and Krafka.[526] However, in evaluating this method of treatment, it should be borne in mind that the administration of vitamin D in large doses over a long period of time may be definitely dangerous, particularly in children and in patients with calcified pulmonary tuberculosis. Thus, blood calcium determination in a number of cases by Wright[970] showed a rapid rise from 9 mg. per 100 cc. to as high as 15 mg. per 100 cc., suggesting the inadvisability of continued use of such massive doses. Moreover, discontinuance of this therapy was often followed by recurrence of the disease. Clarke[999] found that this type of therapy could not be relied upon to control or cause involution of psoriasis lesions. Wright[970] summarizes his experience in the statement that vitamin D cannot in any way be regarded as a specific for psoriasis, that it is expensive and, in view of the marked rise in blood calcium just mentioned, possibly dangerous, if continued over an extended period of time. However, Wright[970] as well as Ebert[442] reported favorable results with high doses of vitamin D in pustular psoriasis, which is notoriously refractory to treatment.

From the various reports of good results achieved with diets extremely low in protein, fat, or salt, we must conclude that the most plausible explanation of the therapeutic effect is as follows: The organism, deprived of its normal supply of vitally essential material, depletes its stored reserves and then, in the absence of adequate synthesis of these substances, must resort to breaking down the cellular material of the psoriatic lesions.

In addition to dietary therapy, the treatment of psoriasis also calls for local measures. Obviously, it is not within the province of this book to present an exhaustive discussion of the topical therapy for this disease. Therefore, mention will be made of only two procedures which the writer himself has most frequently employed with success.

The following ointment, in gradually mounting concentrations, has proved very beneficial when applied to the skin, which has been previously prepared as follows: The skin is covered with a moderately thick layer of green soap, and the patient sits in a warm bath for fifteen minutes; thereupon, the soap is rubbed off in the bath and the patient remains in the same water for another fifteen minutes; then the skin is thoroughly dried, and a thin layer of ointment is carefully rubbed in on all the affected areas, with the exception of the face and scalp. To begin with, ¼ per cent of chrysarobin and 2 per cent tar is used, gradually increased to a maximal

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999. Clarke, G. E.: Arch. Dermat. & Syph. **41**: 664, 1940.

strength of 10 per cent chrysarobin and 10 per cent tar. The urine should be examined once a week for albumin.

		Gm. or Cc.	
℞	Chrysarobin	0.25–10	gr. iv–ʒ iiss
	Oleum rusci	5–10–20	ʒi–iiss–v
	Zinc oxide		
	Talc	aa 10	aa ʒiiss
	White petrolatum	q.s. ad 100.0	q.s. ad ℥iii

In severe cases, the Goeckerman treatment has been found beneficial. O'Leary[1000] gives a detailed description of the manner in which this treatment is administered at the Mayo Clinic. The ointment, consisting of

		Gm. or Cc.	
℞	Crude coal tar	2.0 to 4.0	ʒss to i
	Zinc oxide	2.0	ʒss
	Corn starch	50.0	℥iss
	Petrolatum	q.s. ad 100.0	q.s. ad ℥iii

is applied thickly, and a suit of inexpensive underwear is worn over it. Once a day, all but a thin film of the ointment is removed, and enough ultraviolet light is given through this film to cause a slight erythema. The dose is increased daily to maintain the erythema without vesication. Then the patient spends from thirty minutes to two hours in a bath at 95°F. Thereupon the ointment is again applied. Every other day autohemotherapy is given, the course ending with the fifth treatment. For the scalp, an ointment containing 5 per cent ammoniated mercury and salicylic acid is used instead of the coal tar ointment. This course of treatment necessitates hospitalization for two weeks. Keim's modification for ambulatory patients calls for application of 2 to 10 per cent crude coal tar in a cetyl alcohol emulsion before retiring, followed by a tar bath in the morning. An undiluted solution of coal tar is painted on each lesion prior to ultraviolet irradiation.

Finally, we should like to second the reminder expressed by Pillsbury, Sulzberger, and Livingood:[1001] "Teach the psoriatic to live with his disease and not fight it continuously." The effect of psoriasis on the patient's mental attitude and morale are often more important than the changes in the skin.

1000. O'Leary, P. A.: Canad. M. A. J. **48**: 34, 1943.

1001. Pillsbury, D. M., Sulzberger, M. B. and Livingood, C. S.: Manual of Dermatology. Philadelphia: Saunders, 1942.

CHAPTER XI

Skin Diseases Due to Vitamin Deficiencies

THE relationship between vitamins and the skin was considered in some detail in Chapter III. Here we plan to describe the cutaneous manifestations of the vitamin deficiencies in the light of our present understanding of the subject and to discuss the dietary and vitamin therapy of these conditions.

A. SKIN DISEASES DUE TO VITAMIN A DEFICIENCY

It is becoming increasingly apparent that the skin is closely dependent upon normal vitamin A metabolism, and this despite the paradoxical fact that the epidermis contains practically none of this vitamin (Cornbleet and Popper[385]).

Vitamin A deficiency may lead to changes in proliferation, stratification, and to ultimate keratinization of the epidermis as a result of various pathogenic causes, such as insufficient intake of vitamin A, interference with its absorption and transport, local destruction, and local demand. Moreover, as Sullivan and Evans'[359] painstaking investigations have demonstrated, the cutaneous manifestations may present a variety of pictures, depending on the nature of associated complicating deficiencies of the vitamin B complex, of fat, or of essential fatty acids. Any one of the following conditions may contribute to vitamin A deficiency: liver damage of various degrees, biliary tract disease, diabetes, disturbances of fat metabolism, thyroid dysfunction, prolonged use of mineral oil, constitutional abnormalities, and senescence. It often requires careful clinical and laboratory study to discover the nature of the underlying condition; even then the final answer may often depend on the therapeutic effect of vitamin A itself.

1. FOLLICULAR HYPERKERATOSIS (PHRYNODERMA, KERATOSIS PILARIS)

The skin changes in vitamin A deficiency are characterized by hyperkeratinization of the lining epithelium of the pilosebaceous (Figs. 191, 192) and sweat glands, and were originally termed follicular hyperkeratosis by Stannus.[1002] Nowadays severe cases accompanied by marked dryness and scaliness of the skin (xerosis) are generally called phrynoderma (toad-skin), a term coined by Nicholls.[371] Milder forms, presenting roughness

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1002. STANNUS, H. S.: Trans. Roy. Soc. Trop. Med. & Hygiene 5: 112, 1911–12.

of the skin, particularly on the extensor surfaces of the arms, thighs, and buttocks due to the formation of small papules surrounding follicles filled with keratotic plugs, are designated keratosis pilaris. Lichen spinulosus is an inflammatory disease of the hair follicles, in which a tiny epidermic spur occupies the center of the papule (Crocker[1003]). However, it should be borne in mind that follicular hyperkeratosis is by no means pathognomonic of vitamin A deficiency but may also occur in ascorbic acid deficiency (see p. 480).

The specific cutaneous lesions of vitamin A deficiency, their distribution and histology are fully described on page 155. They were first recognized as characteristic of avitaminosis A by Frazier and Hu.[368] While the fully developed clinical picture is rarely seen in this country, abortive forms, such as keratosis pilaris (lichen pilaris), are quite commonly encountered both in children and in adults. Although it is now generally believed that these symptoms are as a rule due to a diet deficient in vitamin A, Lehman and Rappaport[375a] are of the opinion that one should also consider the possibility of some hereditary disturbance in vitamin A metabolism which might interfere with its utilization and thus increase the minimal requirement for this substance

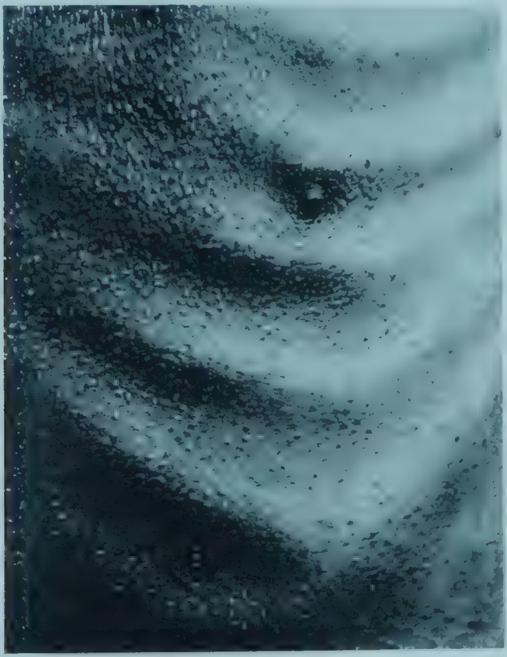

FIG. 191. FOLLICULAR HYPERKERATOSIS

(Courtesy of Dr. C. N. Frazier and the Archives of Dermatology and Syphilology.)

The specific relationship of phrynoderma to hypovitaminosis A is shown first by the frequent occurrence of the lesions of this cutaneous disease in

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1003. CROCKER, H. R.: Diseases of the Skin. Philadelphia: Blakiston, 1908.

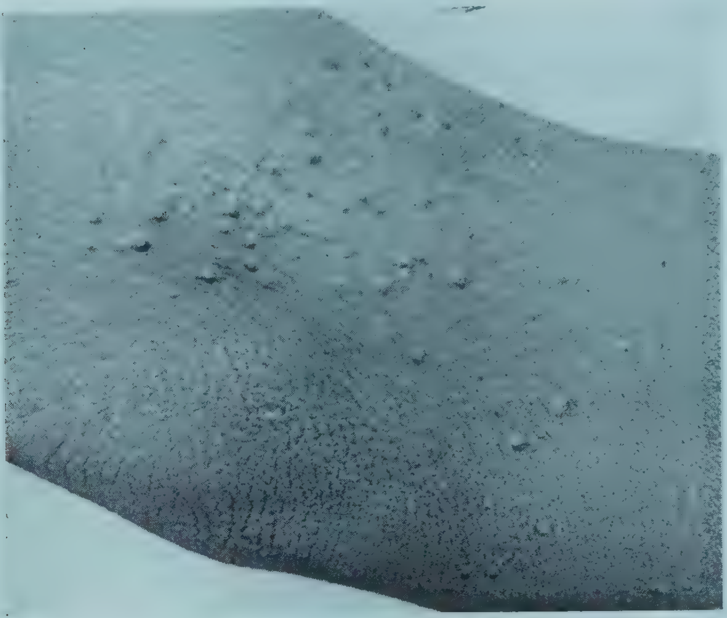

Fig. 192. Phrynoderma

(Courtesy of Dr. P. Fasal and the Archives of Dermatology and Syphilology.)

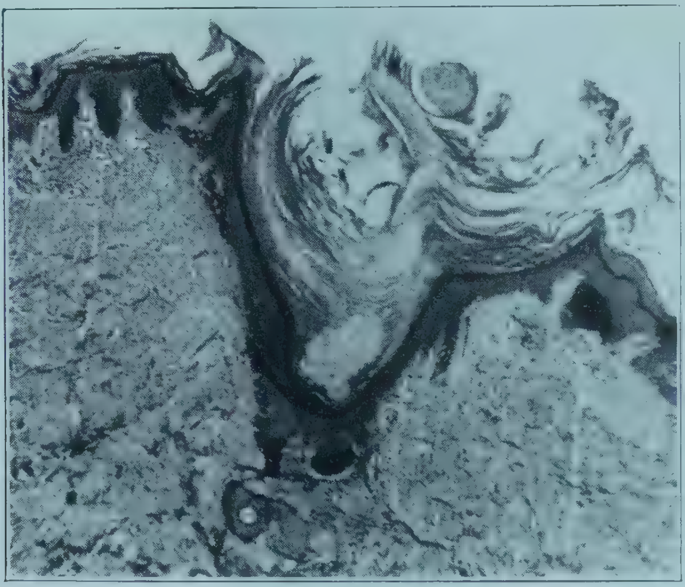

Fig. 192a. Phrynoderma

Histologic section showing excessive keratinization of the mouth of the hair follicle with resultant formation of a plug of laminate keratin (Courtesy Dr. Paul Fasal).

individuals with impaired dark adaptation or night blindness and other signs of an inadequate intake of vitamin A, and second by a good response to vitamin A therapy (Frazier and Hu,[368] Youmans and Corlette,[375] Goodwin,[1004] Strakosch[1005]). Moreover, these lesions have been produced in human beings kept on an experimental vitamin A-free diet (Steffens et al.,[388] Montgomery,[1006] Jeghers[322]).

Keratosis pilaris is a rather common condition. It is questionable, however, whether hypovitaminosis A is its sole or even its most common cause. Frazier[368] assumes the presence of an additional endocrine factor, because the frequency of the follicular lesions increases with the patient's age. Gross[840] saw keratosis pilaris disappear in pregnancy. Other authors have reported improvement following thyroid medication. This may explain why the response to vitamin A therapy is so variable. Thus, in some of Straumfjord's[1007] patients the lesions disappeared in a few months on a daily oral intake of 100,000 U.S.P. units, while in others the condition showed only moderate improvement after four years of continuous treatment.

Lichen spinulosus is a disorder which resembles keratosis pilaris. The affection occurs chiefly in children. The sites of predilection are the extensor surfaces of the arms and thighs, the trochanteric region, the abdomen, and the back of the neck. The lesions, which are pinhead-sized, conical, spinous papules, generally persist indefinitely. Garfield[1008] reported good results from using high doses of vitamin A orally.

Straumfjord[1007] explains the characteristic distribution of the lesions of phrynoderma, keratosis pilaris, and lichen spinulosus on the back, elbows, buttocks, calves of the legs, and posterolateral aspects of the thighs and arms, by the fact that the weight of the body rests on these areas during sleep. Moreover, the lesions also make their appearance in the areas of pressure from brassiere straps in women and from the belt in men. The mechanical pressure of the body's weight serves to diminish the flow of blood and, therefore, the supply of vitamin A to the regions involved, with the results that the lesions appear there.

2. Keratosis Follicularis (Darier's Disease)

This rare disorder is characterized by a symmetrical, fairly well generalized eruption of small, firm papules at the pilosebaceous orifices. The lesions are reddish at first, but become covered by a greasy, grayish, or

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1004. Goodwin, C. P.: Brit. M. J. **2:** 113, 1934.
1005. Strakosch, E. A.: Journal-Lancet **61:** 453, 1941.
1006. Montgomery, H.: discussion to Smith, S. G., Smith, D. T., and Callaway, J. L.: J. Invest. Dermat. **4:** 23, 1941.
1007. Straumfjord, J. V.: Northwest. Med. **41:** 229, 1942.
1008. Garfield, W. T.: Arch. Dermat. & Syph. **45:** 423, 1942.

brownish dust. On the scalp there are fatty crusts very similar to those seen in severe seborrhea. There is also some palmar or plantar keratoderma. The disease is very often hereditary, and is familial in 25 to 50 per cent of the cases (Becker and Obermeyer[269]).

Peck and associates[1009, 392] presented convincing evidence linking the pathogenesis of this disorder to some abnormality of vitamin A metabolism. In eight of ten cases the initial levels of vitamin A in the blood were found to be below normal. However, the carotene content of the blood was within normal limits. In nine of these cases the cutaneous lesions gradually yielded to oral administration of 200,000 U.S.P. units of vitamin A daily. This improvement was preceded by a return of the vitamin content of the blood serum to normal levels. Some patients were rendered virtually free of all lesions after many months of treatment, while others showed decided improvement but did not clear entirely. The lesions of the dorsa of the fingers and on the palms and soles (Figs. 193, 194) were the most apt to resist treatment. When vitamin A therapy was discontinued, recurrences seemed to take place approximately at the sites of the original eruptions. The authors conclude that keratosis follicularis is a vitamin A deficiency disease. There seems to be either a hereditary or an acquired impairment of the capacity to absorb vitamin A or to convert provitamin A into vitamin A, an anomaly which expresses itself in the skin in the form of dyskeratosis.

So many authors (Barwasser,[1010] Cannon,[1011] Sutton, Jr.,[1012] Michelson,[1013,1014] Sweitzer,[1015] Abramowitz,[1016] Haynes,[1017] Eller and Diaz,[530] Welton,[1018] Newman,[1019] Carleton and Steven[1020]) have confirmed the good results achieved by Peck and associates with massive doses of this vitamin administered over a long period of time that it now generally believed that Darier's disease represents a disorder due to abnormal metabolism of vitamin A. It is even claimed that what is inherited is not Darier's disease itself but the metabolic abnormality leading to it. However, the fact that the skin shows marked improvement but does not become entirely normal suggests that impairment of vitamin A metabolism may not be the only factor involved in the pathogenesis of this dermatosis.

[1009] Peck, S. M., Chargin, L., and Sobotka, H.: Arch. Dermat. & Syph. **43:** 223, 1941.
[1010] Barwasser, N. C.: Arch. Dermat. & Syph. **44:** 961, 1941.
[1011] Cannon, A. B.: Arch. Dermat. & Syph. **44:** 1163, 1941.
[1012] Sutton, R. L. Jr.: quoted by Peck et al.[392]
[1013] Michelson, H. E.: Arch. Dermat. & Syph. **45:** 628, 1942.
[1014] Michelson, H. E.: Arch. Dermat. & Syph. **46:** 179, 1942.
[1015] Sweitzer, S. E.: Arch. Dermat. & Syph. **45:** 628, 1942.
[1016] Abramowitz, E. W.: Arch. Dermat. & Syph. **45:** 976, 1942.
[1017] Haynes, H. A. Jr.: Arch. Dermat. & Syph. **47:** 421, 943.
[1018] Welton, D. G.: Arch. Dermat. & Syph. **47:** 398, 1943.
[1019] Newman, B. A.: Arch. Dermat. & Syph. **47:** 288 and 293, 1943.
[1020] Carleton, A. and Steven, D.: Arch. Dermat. & Syph. **48:** 143, 1943.

3. Pityriasis Rubra Pilaris

It is generally accepted that pityriasis rubra pilaris (Devergie) and lichen ruber accuminatus (Kaposi) represent one and the same disorder, characterized by hard, yellowish pink or reddish papules which are situated at the mouths of the hair follicles and oil gland ducts, and which may become generally or even universally distributed (Sutton and Sutton[337]). In addition, there is often palmar or plantar keratoderma, as well as seborrheic dermatitis. The etiology of this disease which runs an intractable course was entirely unknown until quite recently, when Pettler[1021] first demonstrated that great improvement could be achieved by giving large doses of vitamin A. This relationship was clarified largely by the work of Brunsting and Sheard,[1022] who in each of three cases demonstrated impaired dark adaptation which returned to normal threshold levels during the course of appropriate vitamin treatment (150,000 U.S.P. daily). Vitamin A therapy, continued for months, resulted in a slow and definite, but not complete, improvement of the condition of the skin. O'Leary

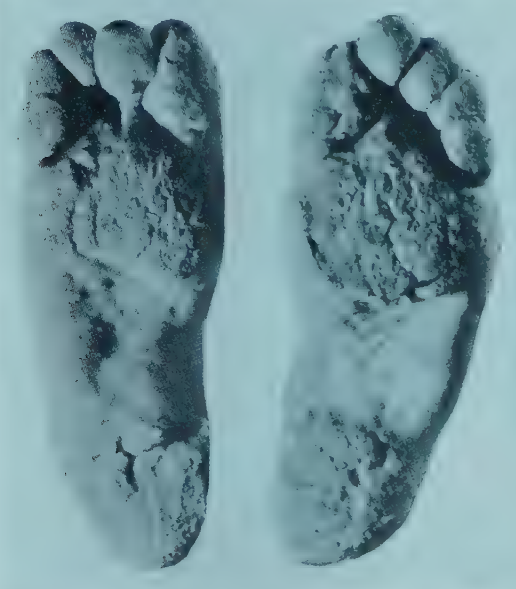

Fig. 193

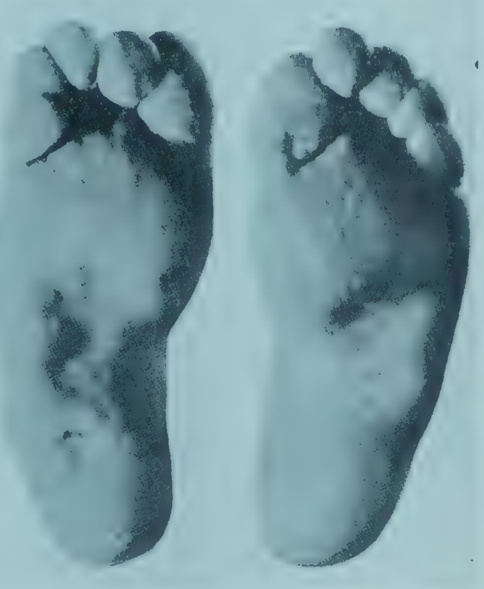

Fig. 194

Darier's Disease

Fig. 193. Lesions on the soles showing marked hyperkeratosis.

Fig. 194. Great improvement in the lesions after five months of intensive vitamin A therapy.

(Courtesy of Dr. S. M. Peck and the Archives of Dermatology and Syphilology.)

[1021] Pettler, M. F.: Pennsylvania M. J. 39: 864, 1936.

[1022] Brunsting, L. A. and Sheard, C.: Arch. Dermat. & Syph. 43: 42, 1941.

and co-workers[1023] reported a child who was greatly benefited by this means. On three occasions the vitamin A therapy was stopped for a month, with a recurrence each time of the waxy palms and soles and, just as regularly, there was disappearance of the lesions after resumption of the therapy. A number of other authorities, including Peck and Chargin,[1024] Traub,[1025] Ebert,[442] Weiner and Lewin,[1026] and Ormsby[1027] have reported similar results. A pertinent case observed by C. C. Thomas is shown in Figures 195 and 196.

In contradistinction to the authors mentioned above, Gross[1028, 1029] is of the opinion that, because of the response to niacin, yeast, and liver therapy, pityriasis rubra pilaris is caused by a complex deficiency rather than by avitaminosis A alone. He submits the hypothesis that a combined vitamin A and B complex deficiency is the cause of this skin disorder.

O'Leary[1030] believes that there are pathogenically two types of pityriasis rubra pilaris. The patients who are improved by vitamin A therapy are demonstrably afflicted with night blindness. In the other group, composed of individuals with normal dark adaptation, he assumes the presence of a complex deficiency similar to that postulated by Gross.

Lastly, Brunsting advocates intramuscular injections of 20,000 U.S.P. units of vitamin A two or three times a week for two months—a therapy which in his opinion is more effective than the usual procedure of administering 200,000 to 400,000 U.S.P. units daily, by mouth, for a period of four months.

4. ICHTHYOSIS

Ichthyosis simplex is a congenital cutaneous disease characterized by dry, rough, scaly skin, with diminished activity of the sebaceous and sweat glands, and associated with abnormal cornification. A hereditary tendency is often noted.

Cod liver oil has long been used empirically in the treatment of ichthyosis, and the writer has employed it in mild cases with very satisfactory results. Sulzberger,[1031] Baer and Vogel[1031a] and Vail[1031b] noted clinical and biophotometric improvement in a number of patients treated with 10,000

1023. O'Leary, P. A., Montgomery, H., and Brunsting, L. A.: Arch. Dermat. & Syph. **50:** 211, 1944.
1024. Peck, S. M. and Chargin, L.: Arch. Dermat. & Syph. **44:** 722, 1941.
1025. Traub, E. F.: Arch. Dermat. & Syph. **45:** 1012, 1942.
1026. Weiner, A. L. and Levin, A. A.: Arch. Dermat. & Syph. **48:** 288, 1943.
1027. Ormsby, O. S.: Michigan State M. J. **43:** 315, 1944.
1028. Gross, P.: Arch. Dermat. & Syph. **44:** 270, 1941.
1029. Gross, P.: Arch. Dermat. & Syph. **44:** 751, 1941.
1030. O'Leary, P. A.: Arch. Dermat. & Syph. **47:** 463, 1943.
1031. Sulzberger, M. B.: 1938 Year Book of Dermatology and Syphilology. Chicago: Year Book Publishers, 1939.
1031a. Baer, H. L. and Vogel, H. .: Urol. & Cutan. Rev. **44:** 176, 1940.
1031b. Vail, D.: Arch. Ophth. **24:** 215, 1940.

to 30,000 U.S.P. units daily of vitamin A for several months. However, the most exhaustive work in this direction has been done by Rapaport and co-workers.[1032] They summarize the points suggestive of a close connection between ichthyosis and avitaminosis A as follows: Frequent association in the same patient with the follicular keratotic lesions of avitaminosis A; the presence of ichthyosis lesions on the legs of patients in published illustrations depicting the characteristic skin lesions of vitamin A deficiency; a seasonal fluctuation, with great amelioration or even complete clearing of symptoms during the summer, in both ichthyosis and phrynoderma (improvement of these conditions has been explained by the great vitamin A content of foods during the spring and summer

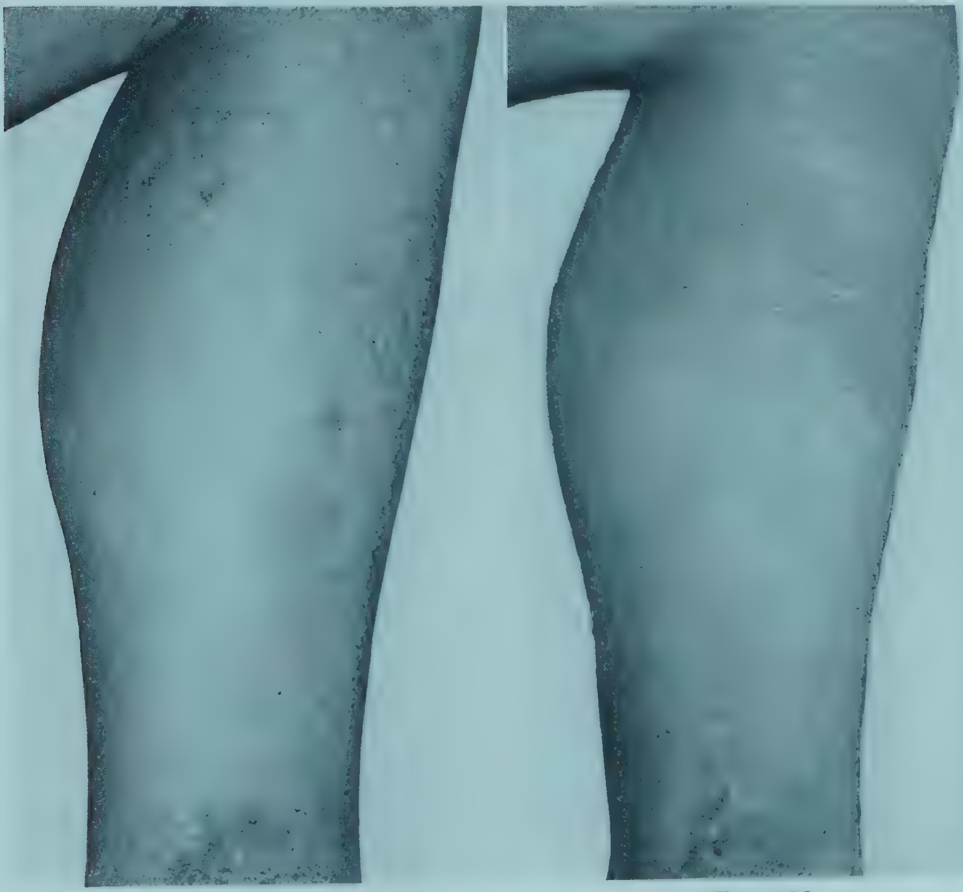

Fig. 195 Fig. 196

Pityriasis Rubra Pilaris

Fig. 195. Before treatment.

Fig. 196. After four months of intensive vitamin A therapy (200,000 U.S.P. units daily).

(Courtesy of Dr. C. C. Thomas.)

[1032] Rapaport, H. S., Herman, H., and Lehman, E.: J. Pediat. 21: 733, 1942.

months); frequent delay in the first appearance of ichthyosis until after weaning; marked dryness of the skin in both conditions, with deficiency or absence of sweat gland and sebaceous gland secretions; a predilection for involvement of the same regions of the skin in both disorders; and similarity in the histopathology of the skin in ichthyosis and avitaminosis A.

Rapaport[1032] reported definite improvement following prolonged and intensive vitamin A therapy. In some cases, however, it was found that the condition responded only when the treatment was administered via the intramuscular route, using 100,000 U.S.P. units two or three times weekly for several months. According to Rapaport, such a response to parenteral therapy suggests a defective absorption of vitamin A from the gastrointestinal tract.

Peck and associates[1033] described two cases of ichthyosis showing low vitamin A levels in the blood. Administration of 200,000 U.S.P. units promptly raised the blood vitamin A level, but the clinical picture showed no improvement. While there is evidently some disturbance of the vitamin A metabolism involved here, the relationship of the cutaneous manifestations to the metabolic anomaly is not entirely clear. The fact that even in those cases which show a definite response to therapy the skin never becomes entirely normal certainly suggests the probability that some other factor, possibly also nutritional, plays an accessory role in the etiology of icthyosis.

In conclusion, Rapaport believes that ichthyosis is fundamentally due to some hereditary disturbance of vitamin A metabolism which interferes with its utilization and raises the minimal requirement for this substance. He and his co-workers interpret the hereditary mechanism so often present in icthyosis as one involving the inheritance of some disorder of vitamin A metabolism, rather than inheritance of the abnormal ichthyotic skin. In other words, as Jeghers[322] put it, the patient develops ichthyosis because he inherited the inability to absorb or metabolize vitamin A properly.

5. Sjögren's Syndrome

In 1933, Sjögren[366] described a syndrome characterized by pronounced dryness of all the mucous membranes, which is due to inadequate secretion by the glands involved, particularly the lachrymal and salivary glands, the mucous glands of the upper respiratory tract, the sweat glands, and the secretory apparatus of the stomach. This leads to inadequate lachrymation, keratoconjunctivitis sicca, xerostoma, rhino-pharyngo-tracheobronchitis sicca with marked dysphagia, husky voice, impairment of the senses of taste and smell, inadequate perspiration, and achylia gastrica. There are also disturbances in the carbohydrate tolerance, general weakness, lack of appetite and anemia. This disease seems to affect almost exclusively women past the menopause, particularly those suffering from rheumatoid arthritis. Some cases exhibit bilateral swelling of the parotid glands according to Bruce,[1034] who also observed that dryness confined to the cornea and conjunctivae and to the oral and upper respiratory mucous membranes is more commonly encountered than the entire syndrome. Sheldon[1035] reported a patient who presented, in addition, hyperkeratoses on the soles, deep pigmentation of the legs associated with numerous small telangiectases, and a number of the latter on the face as well.

[1033] Peck, S. M., Glick, A. W., and Chargin, L.: Arch. Dermat. & Syph. 48: 32, 1943.

Stahel[1036] considers Sjögren's syndrome to be a manifestation of vitamin A deficiency with consequent disturbances in the ectodermal and endodermal tissues. He treated his patients with vitamin A and noted striking improvement after a few months. Sulzberger[1037] had similar success to report.

6. Miscellaneous Skin Conditions Attributed to Vitamin A Deficiency

Under this heading we shall discuss briefly several observations which show how important vitamin A therapy has become in the management of dermatoses. Vitamin A is beneficial in the treatment of diseases characterized by excessive or abnormal keratinization, either localized or diffuse, even when the underlying inflammatory dermatosis does not in itself appear to be one in which this form of therapy is indicated. But we must not fail to point out that, as far as most of the dermatoses mentioned below are concerned, the number of cases treated or reported has been too small to warrant definite conclusions.

Combes and Behrman[1038] reported successful treatment of a case of keratosis blennorrhagica with massive doses of vitamin A (200,000 U.S.P. units daily). After two weeks there were spectacular changes, and after five weeks the lesions had disappeared. Straumfjord[1007] noted that corns and callosities disappeared under this treatment, but he stresses that high doses of vitamin A must be given for many months and sometimes even for two or three years. Broadly speaking, this category comprises the gratifying results obtained in leukoplakia (Swift[1039]), kraurosis vulvae (Swift[1039]), and senile vaginitis (Simpson and Mason[1040]).

1034. Bruce, G. M.: Arch. Ophth. **26:** 945, 1941.
1035. Sheldon, J. H.: Proc. Roy. Soc. Med. **32:** 255, 1939.
1036. Stahel, W.: Klin. Wchnschr. **17:** 1692, 1938.
1037. Sulzberger, M. B.: in discussion to Gross[1028].
1038. Combes, F. C. and Behrman, H. T.: Arch. Dermat. & Syph. **46:** 728, 1942.
1039. Swift, B. H.: J. Obst. & Gynaec. Brit. Emp. **43:** 1053, 1936.
1040. Simpson, J. W. and Mason, K. E.: Am. J. Obst. & Gyn. **32:** 125, 1936.

Markowitz[43] describes improvement in a girl with xeroderma pigmentosum. Sulzberger[1041] found vitamin A to be beneficial in certain forms of brittleness of the nails. The present writer had a similar experience with three such cases. Hall[1042] observed a favorable response in dermatitis papillaris capillitii. In two cases of unusually hyperkeratotic lichen simplex chronicus which had proved refractory to all other forms of treatment, Obermayer and Frost[1043] achieved striking improvement with vitamin A therapy.

Gross[877] reports that vitamin A has a favorable action on the therapeutic response of nummular dermatitis (see p. 365), chiefly by influencing the asteatosis which is a predisposing cause in this type of dermatitis.

Kuipers[1043a] found that there is a definite connection between the course of seborrheic infantile dermatitis and the vitamin A content of the blood. When vitamin A was given in doses sufficient to increase the level in the blood the cutaneous lesions promptly cleared, but, on the other hand, when the concentration of the vitamin in the blood fell the clinical picture worsened. The decrease in the blood vitamin A content is perhaps the result of impaired absorption of this vitamin from the intestinal tract, as observed by di Sant' Agnese and Larkin[906] in four infants with intractable dermatitis.

Straumfjord[1043b] treated one hundred acne cases with 100,000 U.S.P. units of vitamin A daily for six months, and claims that the lesions disappeared in 79 per cent of these patients. Obermayer and Frost[1043] state that vitamin A is helpful in the management of those forms of acne vulgaris which are characterized by marked follicular plugging, in addition to the formation of comedos. The beneficial effect of vitamin A here becomes readily comprehensible when one recalls that this pathologic feature is identical with the hyperkeratosis of the pilosebaceous follicles seen in avitaminosis A. However, these authors have not been able to confirm Straumfjord's claim that the great majority of acne cases respond to this therapy.

Straumfjord[391] regards vernix caseosa as a manifestation of vitamin A deficiency in the newborn. He reported a number of cases in which large doses of vitamin A given to the mothers during the last six months of pregnancy served to decrease the amount of vernix. However, until more convincing proof is submitted, we are reluctant to consider this rather common condition a manifestation of avitaminosis A.

[1041] SULZBERGER, M. B.: in discussion to Brunsting et al.[1022].

[1042] HALL, T. B.: Arch. Dermat. & Syph. **33**: 880, 1936.

[1043] OBERMAYER, M. E. and FROST, K.: Arch. Dermat. & Syph. **51**: 309, 1945.

[1043a] KUIPERS, F. C.: Acta neerl. Physiol. **1**: 37, 1931.

[1043b] STRAUMFJORD, J. V.: Northwest Med. **42**: 219, 1943.

B. SKIN DISEASES DUE TO VITAMIN B DEFICIENCIES

1. Cheilosis and Angular Stomatitis (Perlèche)

Cheilosis (Fig. 197) is a condition which generally begins with a small red patch at the angles of the mouth. The lesion, often referred to as angular stomatitis, when restricted to the angles of the mouth (Fig. 198) is bilateral and symmetrical. In cases of severe vitamin B deficiency, it rapidly spreads laterally, producing a wet, macerated, yellow, crusted patch about 1.5 cm. in diameter. Later the superficial ulceration disappears, leaving a uniformly red, eroded area, with exaggerated transverse markings, especially on the lower lip.

As early as 1912 Stannus[1002] suggested that nutritional disturbances might be the cause of the various changes of the lips called cheilosis or cheilitis. However, Sebrell and Butler[418] were the first to demonstrate that experimental riboflavin deficiency in man can cause the condition and that the lesions disappear when riboflavin is added to the diet. Although Sydenstricker,[1044] Spies,[1045] Jeghers,[1046] and others have confirmed the fact that the changes of the lips in cheilosis can be caused by ariboflavinosis, we now know that it is not always due to this type of deficiency. Smith and Martin[455] as well as Machella[456] reported excellent results in this condition with pyridoxine therapy. In occasional instances, the lesions fail to respond either to riboflavin or to pyridoxine, but yield to niacin or to calcium pantothenate (Field and associates[1047]). Still other cases may require the entire vitamin B complex in the form of yeast or liver extract (Machella and McDonald,[1048] Gross[840]). More recent studies indicate that cheilosis may be due to multiple deficiencies. It has been suggeted that both pyridoxine and pantothenic acid are essential to the normal metabolism of riboflavin, a view which affords a possible explanation of the inconstant response in cheilosis to riboflavin therapy alone (Jeghers[322]).

It may be interesting to note that ascorbic acid was found to be effective in curing the cheilitic lesions in three patients with scurvy (Machella and McDonald[1048]). In many cases, however, these labial manifestations fail to respond to any kind of vitamin therapy. This is easy enough to understand, because particularly the cutaneous changes in the vicinity of the angles of the mouth known as perlèche* may be due to a number of

* From the French word *pourlecher*, to lick.

1044. Sydenstricker, V. P., Geeslin, L. E., Templeton, C. M. and Weaver, J. W.: J. A. M. A. **113:** 1697 1939.

1045. Spies, T. D., Bean, W. B., Vilter, R. W., and Huff, N. E.: Am. J. M. Sc. **200:** 697, 1940.

1046. Jeghers, H.: Riboflavin Deficiency; in Advances in Internal Medicine. New York: Interscience Pub. Co., **1:** 247, 1942.

1047. Field, H. Jr., Green, M. E., and Wilkinson, C. W. Jr.: Am. J. Digest. Dis. **12:** 246, 1945.

1048. Machella, T. E. and McDonald, P. R.: Am. J. M. Sc. **205:** 214, 1943.

different causes. As Finnerud[1049] recently pointed out, these cases fall into four major groups from the pathogenetic viewpoint: (1) infectious perlèche, either of local bacterial etiology (generally streptococcic or staphylococcic) or of mycotic origin (generally monilial); (2) mechanical per-

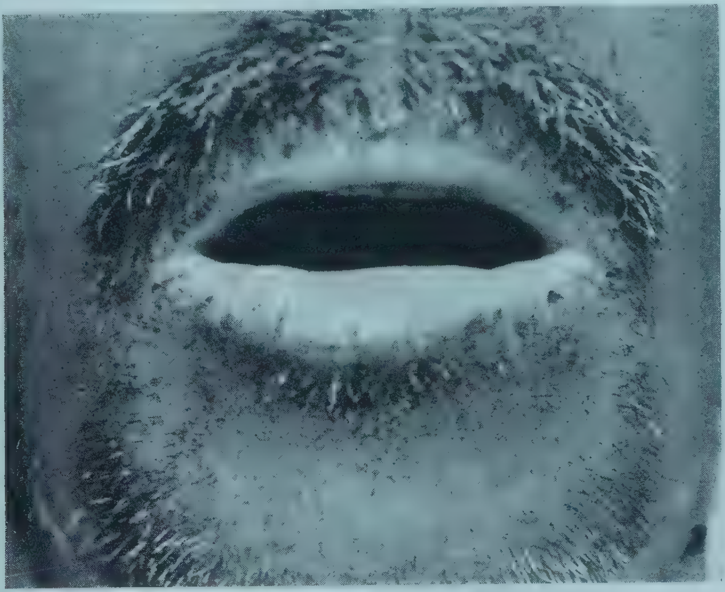

FIG. 197. CHEILOSIS DUE TO RIBOFLAVIN DEFICIENCY

(Courtesy of Dr. P. Fasal.)

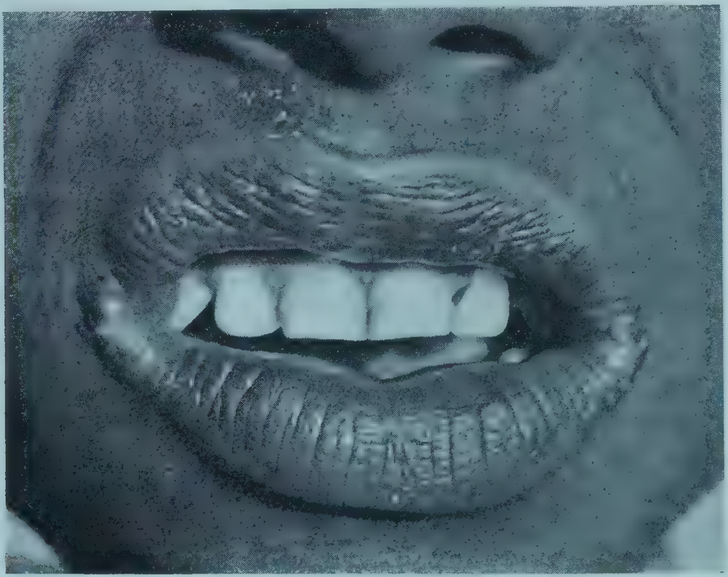

FIG. 198. ANGULAR STOMATITIS DUE TO RIBOFLAVIN DEFICIENCY

(Courtesy of Dr. P. Fasal.)

[1049] FINNERUD, C. W.: J. A. M. A. **126**: 737, 1944.

lèche, occurring in persons with malocclusion (e.g., narrowed bite), or resulting from ill-fitting artificial dentures, or appearing in the aged in whom atrophy of the tissues has led to some overhanging of the upper lip at its lateral margins; (3) vitamin-deficiency perlèche, discussed above; and (4) idiopathic perlèche, in which no etiologic factor can be determined.

While these remarks on perlèche pertain only to those manifestations of cheilosis which refer to angular stomatitis, it should be noted that changes of the lips can be caused by factors other than vitamin deficiencies. Thus, Sulzberger and Goodman[1050] emphasize the importance of hypersensitiveness to lipstick as a cause of cheilitis in women. Other reported allergies include cheilosis due to tooth paste (Beinhauer[1051]), mouth washes (Mumford[1052]), chewing gum (Miller[1053]), throat lozenges (Templeton[1054]), dental plates (Cole and Driver[1055]), cigarette holders (Mumford[1052]), and the wooden mouthpiece of a musical instrument (Lerner[1056]). Lastly, cheilosis may be caused by sunlight (Ayres, Jr.[1057]) as well as by strong artificial light such as carbon arc light (Urbach)

Since cheilosis and related labilial conditions have a varying pathogenesis, it seems advisable to follow Obermayer and Frost's[1043] suggestion to rule out infectious, allergic, anatomic, or mechanical causes before instituting vitamin treatment. When the latter therapy is decided upon, a trial should first be made with riboflavin (5 mg. three times daily). If there is no response within ten to fourteen days, pyridoxine (100 mg. daily) should be given intravenously for at least one week. Should the lesions fail to respond to this treatment, nicotinamide (100 mg. three times a day for a week) and finally the entire vitamin B complex, in the form of liver extract (3 cc. of the crude extract subcutaneously, three times weekly) or brewers' yeast (1 heaping tablespoonful, three times a day) are well worth trying.

2. Pellagra

Pellagra (*pelle agra* = rough skin) has been described as a disease of the three D's: dermatitis, diarrhea, dementia. However, as Spies[124] points out, this combination is not too frequently observed, since it occurs only in the advanced stages of the disease. Mild cases often present only one or two of these signs, sometimes without skin manifestations. The latter are termed "pellagra sine pellagra."

Here we are chiefly interested in the cutaneous aspects of the disorder.

1050. Sulzberger, M. B. and Goodman, J.: Arch. Dermat. & Syph. **37:** 597, 1938.
1051. Beinhauer, L. G.: Arch. Dermat. & Syph. **41:** 892, 1940.
1052. Mumford, P. B.: Practitioner **143:** 612, 1938.
1053. Miller, J.: J. A. M. A. **116:** 131, 1941.
1054. Templeton, H. J.: Arch. Dermat. & Syph. **42:** 138, 1940.
1055. Cole, H. N. and Driver, J. R.: Arch. Dermat. & Syph. **37:** 338, 1938.
1056. Lerner, C.: Urol. & Cutan. Rev. **45:** 195, 1941.
1057. Ayres, S. Jr.: J. A. M. A. **81:** 1183, 1923.

The skin lesions are characteristic and diagnostic, especially when found in a patient with a history of dietary deficiency. The lesions are of various types and may be placed in the following five subdivisions:

1. Dermatitis on the exposed areas of the body. This is provoked by exposure to radiant heat, particularly sunlight, and occurs chiefly on the face (Figs. 199, 200), neck (so-called "necklace" or Casal's collar in the "V" of the neck, Figs. 201, 202), back of hands, forearms, dorsum of feet. However, the dermatitis may occur at sites never exposed to light but exposed to pressure, as on the shoulders, buttocks, knees (Figs. 203), heels, and elbows (Fig. 204) in bedridden patients, or to friction, as in the axillae, thighs, under the breasts, and in the perianal region. The acute lesion in the early stages consists of a sharply delineated, symmetrical, bright red erythema (Figs. 205, 206) resembling sunburn which subsequently presents bullae and ultimately crusting (Figs. 207, 208) and desquamation. This inflammatory reaction is followed by a dusky reddish brown pigmentation and exfoliation. Chronic lesions become thickened, indurated, scaly, and pigmented (Fig. 209.)

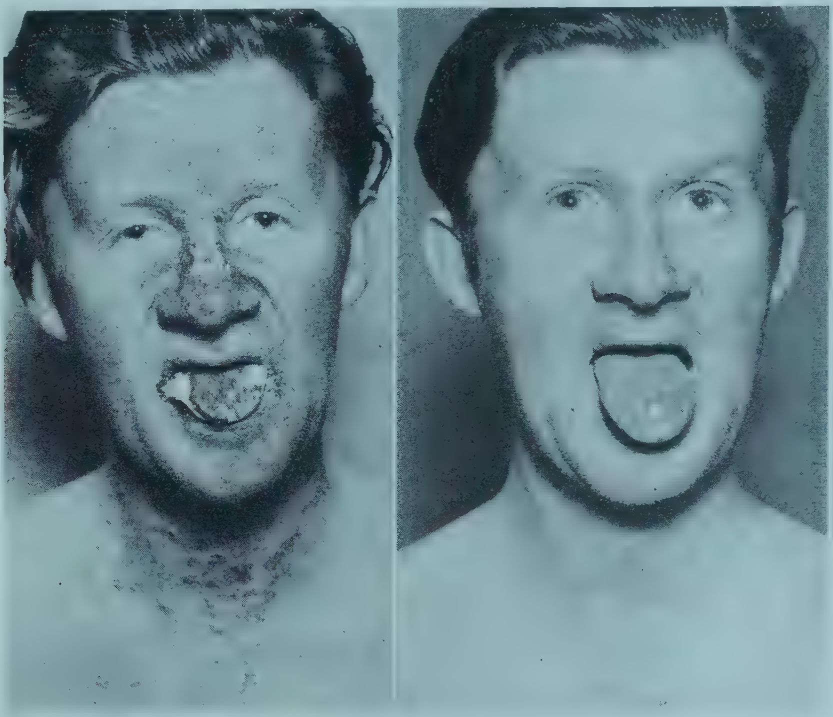

Fig. 199 Fig. 200

Pellagra Showing Typical Changes of the Tongue and over the Bridge of the Nose; also Cheilosis

Fig. 199. Before treatment.

Fig. 200. Six days after treatment with niacin.

(Courtesy of Dr. J. M. Ruffin.)

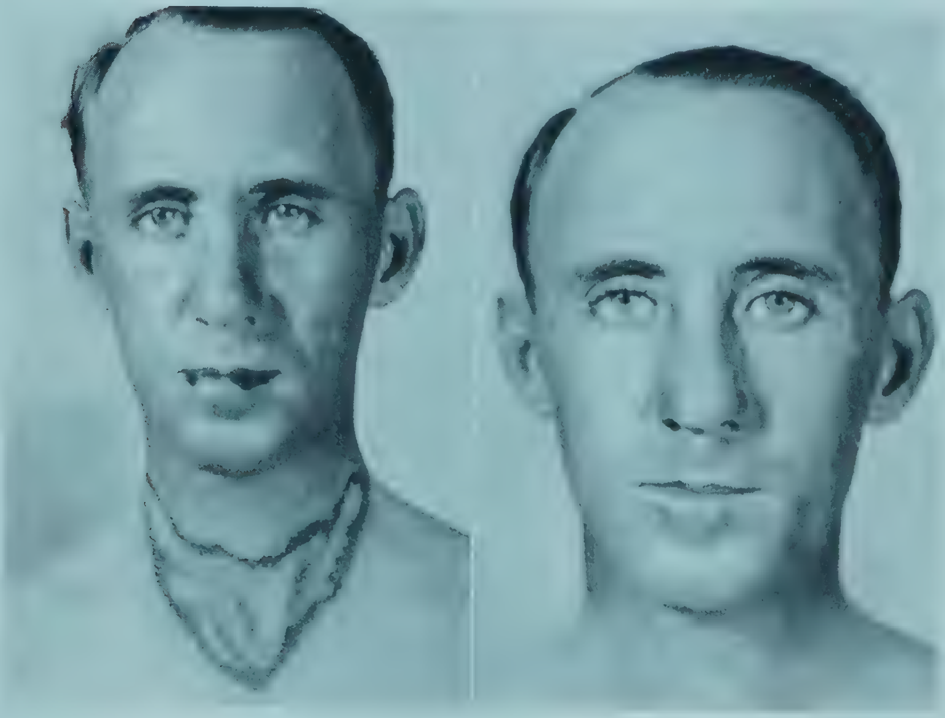

FIG. 201 FIG. 202

PELLAGRA: TYPICAL CASAL'S COLLAR

FIG. 201. Before treatment.
FIG. 202. After vitamin therapy.

(Courtesy of Dr. J. M. Ruffin.)

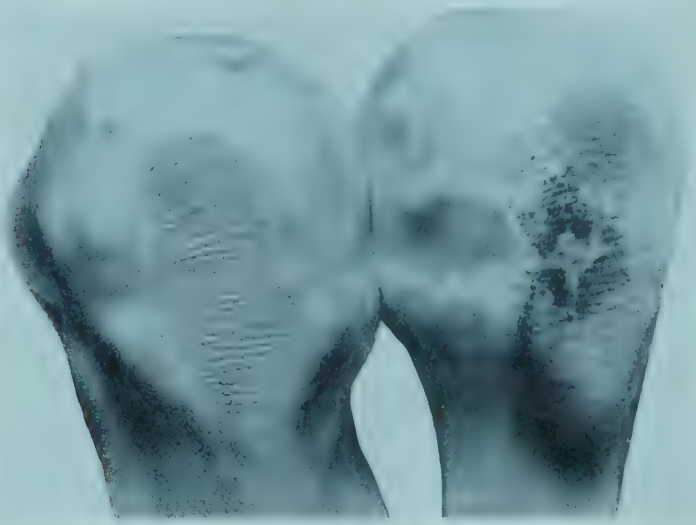

FIG. 203. PELLAGRA: MANIFESTATIONS ON THE KNEES

Thickening and roughening over bony prominences sometimes may be seen in the absence of typical skin lesions.

(Courtesy of Dr. J. M. Ruffin.)

2. A true "dyssebacea," sometimes mislabeled seborrhea. This type is characterized by plugging of the orifices of the sebaceous glands with dry, grayish yellow material which generally projects above the surface of the skin, which therefore feels like sandpaper or sharkskin (Fig. 210). These manifestations make their first appearance about the alae nasi, then spread over the nose and the upper lips and, in advanced cases, to the forehead and chin, involving the whole face. According to Smith,[348] the dyssebacea sometimes appears weeks or even months before the characteristic dermatitis of pellagra develops and is most commonly encountered in alcoholic patients. These lesions heal rapidly (in four to six days) following administration of autoclaved yeast or of crude aqueous extracts of liver. They also respond, but less promptly, to treatment with niacin. Riboflavin therapy alone brings about some improvement but does not induce complete healing unless supplemented with niacin. Smith and co-workers[1057a] believe that the changes in the sebaceous glands are probably due to an associated or mixed deficiency.

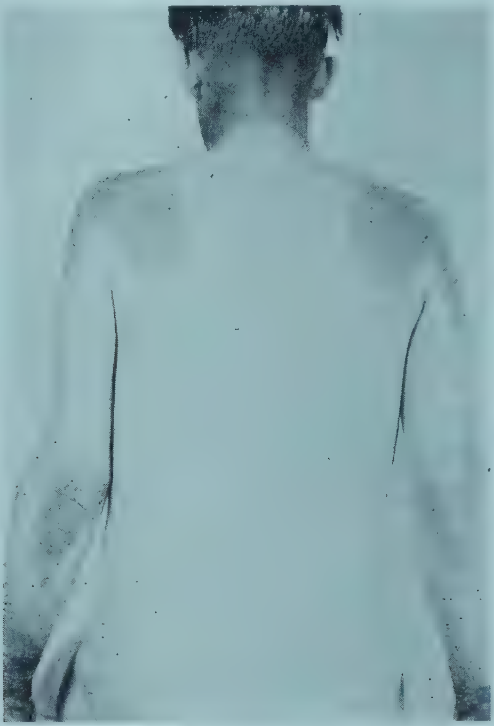

FIG. 204. PELLAGRA: LESIONS ON SHOULDERS AND ELBOWS

(Courtesy of Dr. J. M. Ruffin.)

3. Symmetrical hyperkeratosis with pigmentation. This type is found

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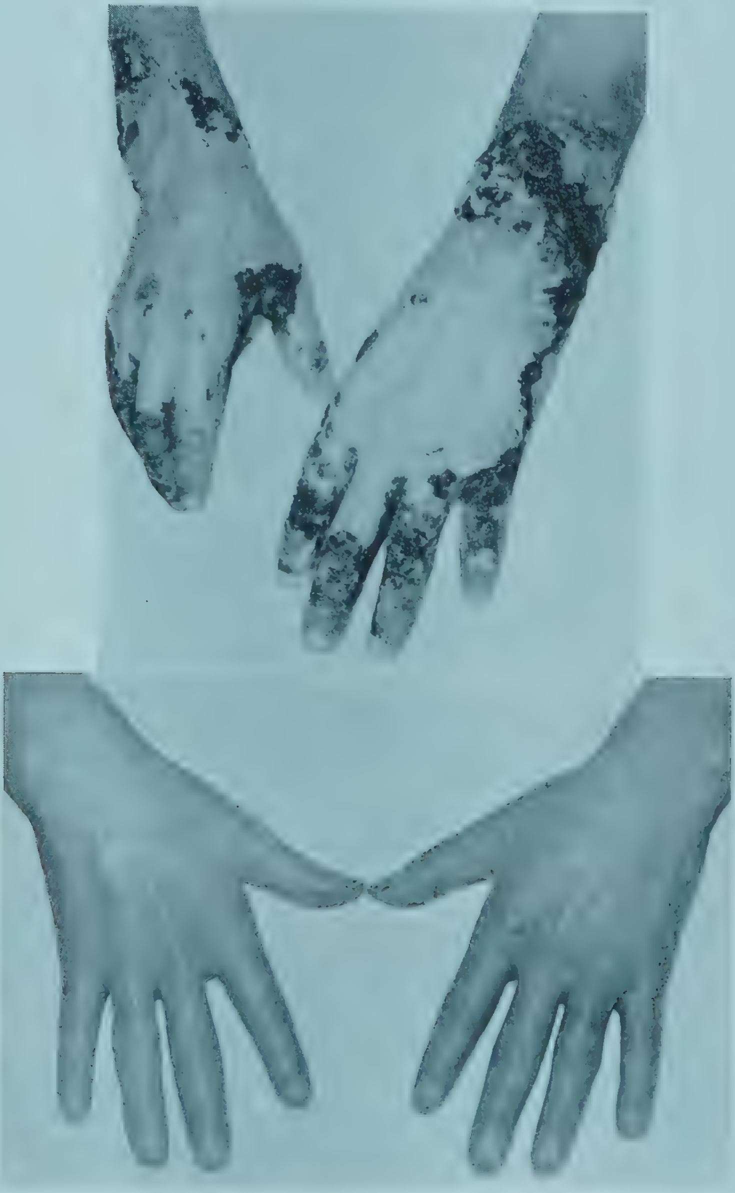
[1057a] SMITH, S. G., SMITH, D. T., and CALLAWAY, J. L.: J. Invest. Dermat. 4: 23, 1941.

in patients on diets deficient in niacin and who have been bedridden for weeks or months.



Pellagra: Severe Dermatitis of Hands
Note symmetrical involvement and sharp delineation.
Fig. 205 (Upper). Before treatment.
Fig. 206 (Lower). After vitamin therapy.
(Courtesy of Dr. D. T. Smith.)

4. Lesions in the genital regions. When the tongue and mucous membranes of the mouth become inflamed, there may be corresponding changes in the mucosa of the vagina and rectum. These perianal lesions (Figs.

211, 212) are red and macerated, and invariably show secondary infection. Scrotal dermatitis is relatively rare.

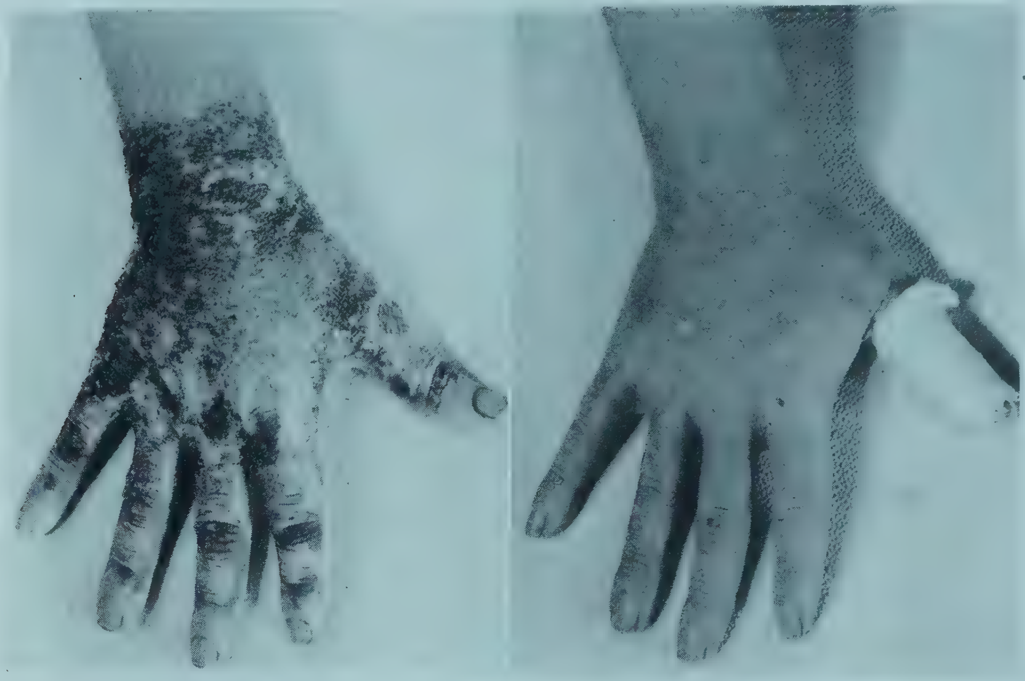


Fig. 207 Fig. 208

Pellagra: Severe Dermatitis of Hands

Later stages showing crusting and desquamation.

Fig. 207. Before treatment.

Fig. 208. After vitamin therapy.

(Courtesy of Dr. J. M. Ruffin.)

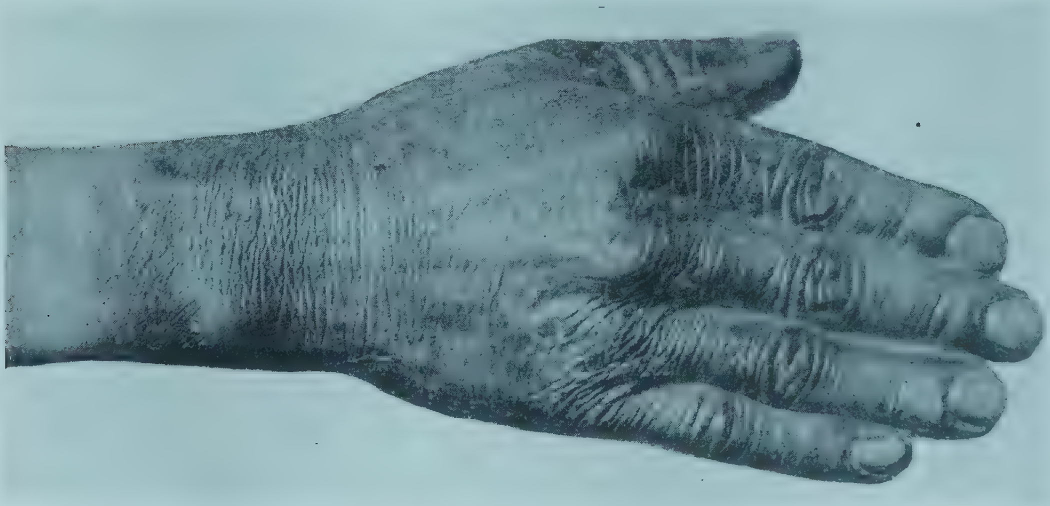


Fig. 209. End Stages of Chronic Pellagra of Hands

Note atrophy of epidermis and deep pigmentation.

5. *Labial manifestations.* The lips are red and scaly and in the corners of the mouth at the mucocutaneous junction there appear fissures and

superficial ulcerations (Fig. 213) associated with scaly lesions in the orifices of the nose and on the ears. These cutaneous changes are often due to an associated riboflavin deficiency and will therefore not yield to treatment with niacin alone. Other cases respond readily to pyridoxine.

Symptoms pertaining to the gastrointestinal tract in pellagra include anorexia, glossitis, and stomatitis. The tongue is usually scarlet red, swollen, somewhat painful, showing indentations at the sides made by the teeth. The papillae of the tongue become atrophic (Figs. 214, 215). The mucous membranes of the mouth are also scarlet red, often with superimposed red patches of Vincent's infection (Jolliffe and Most[1057b]). Diarrhea is commonly but not invariably present. The stools often have a peculiar, foul odor resulting from putrefactive and inflammatory changes in the intestines and frequently contain mucus and partially digested food. The disputed question of a relationship between porphyrin and pellagra was discussed on page 178.

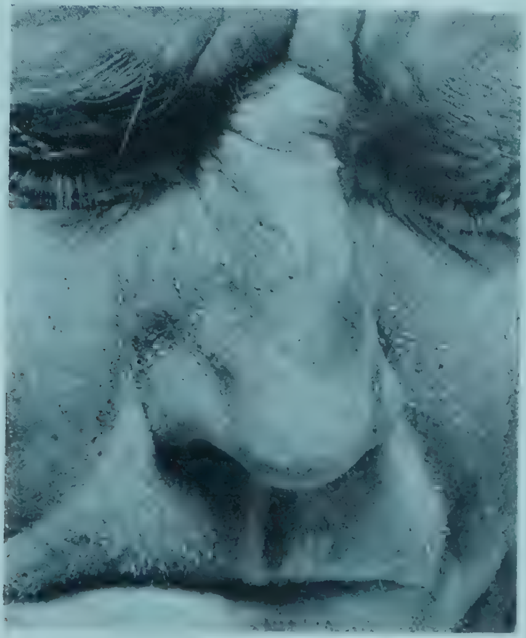


FIG. 210. "DYSSEBACEA" IN PELLAGRA

Plugs in the sebaceous glands of the nasolabial folds are thought to indicate a riboflavin deficiency but often clear up under nicotinic acid therapy alone. Most rapid recovery takes place after treatment with crude liver extract or brewers' yeast.

(Courtesy of Dr. J. M. Ruffin.)

The mental symptoms include nervousness, insomnia, headaches, dizziness, disorientation, emotionalism, confusion, and, in the advanced stages

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1057b. **Jolliffe**, N. and **Most**, R. M.: Appraisal of Nutritional Status; in Vitamins and Hormones. New York: Academic Press, Inc., 1943.

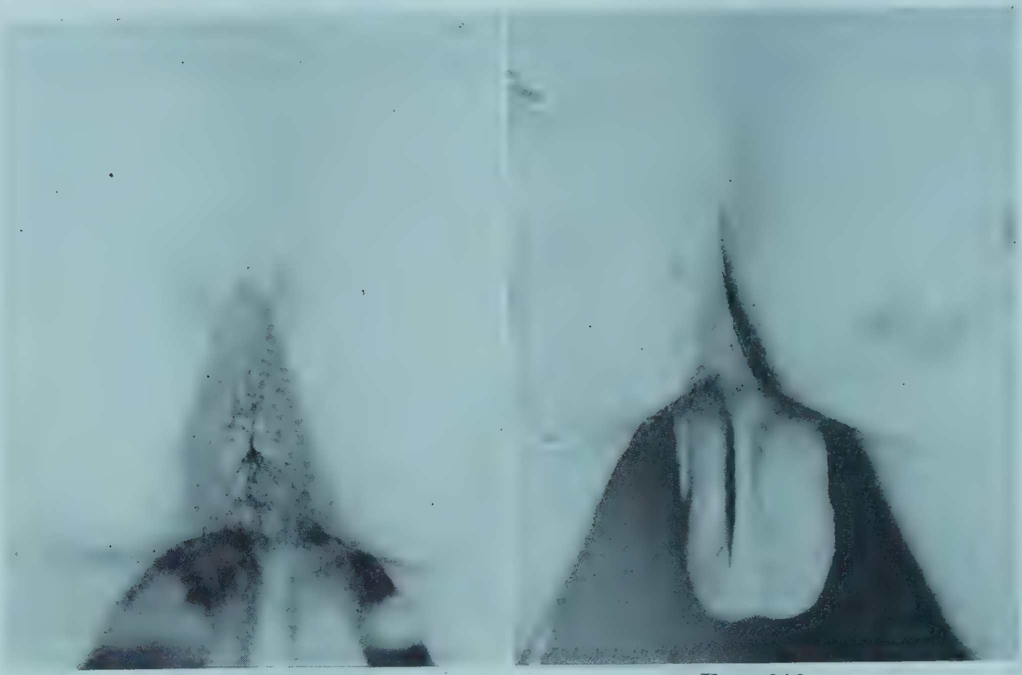


Fig. 211 Fig. 212

Pellagra: Perianal Lesions

Fig. 211. Before treatment.
Fig. 212. After vitamin therapy.
(Courtesy of Dr. J. M. Ruffin.)

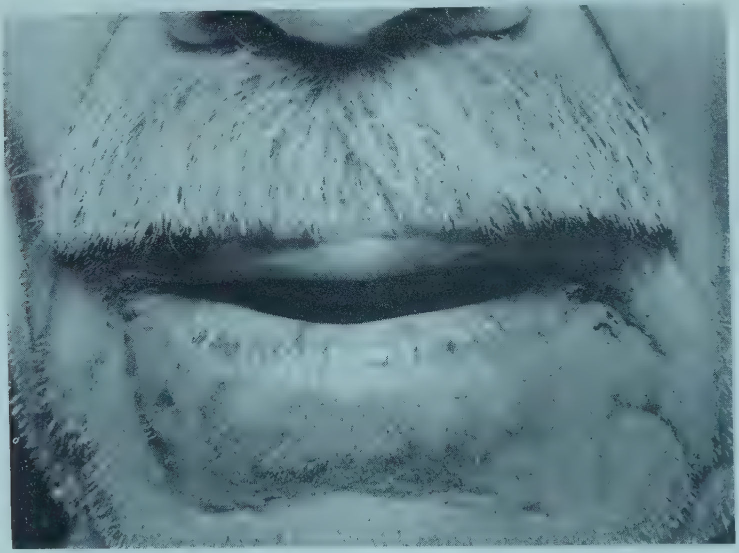


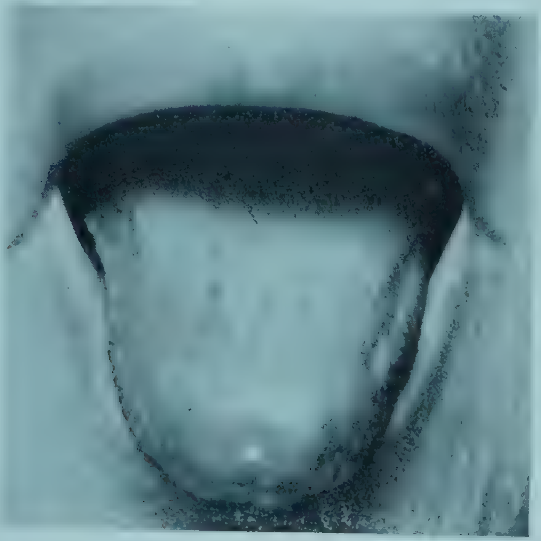
Fig. 213. Cheilosis and Angular Stomatitis Accompanying Pellagra

These may be due to an associated riboflavin deficiency but can occur in niacin deficiency as well.

(Courtesy of Dr. D. T. Smith.)

of the disease, mental states comparable to psychoses. The earliest signs of neuritic symptoms are "burning" pains in the hands and feet. Peripheral neuritis may develop.

Cases may be graded into three groups, according to severity and course. The severe, acute form of pellagra is characterized by dermatitis, glossitis, stomatitis, diarrhea, and mental disturbances, often delirium. There may be fever and extreme prostration, ending with death. Although such symptoms may appear to develop suddenly, they are almost always preceded by a prodromal period during which the patient has various digestive and nervous manifestations.



PELLAGRA: APPEARANCE OF THE TONGUE

FIG. 214. Pellagrous tongue showing marked atrophy at tip and margins.

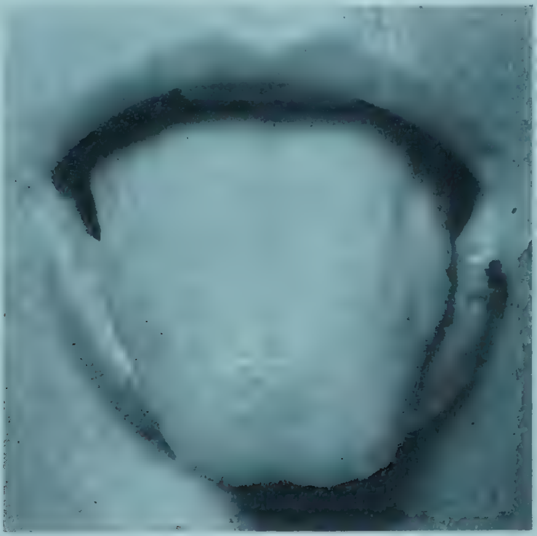


FIG. 215. Normal tongue presented for comparison.

(Courtesy of Dr. D. T. Ruffin.)

In addition to these severe, acute cases there are many in which the disease is much milder, although the typical and easily recognizable signs are present. Cases of this kind are distinguished by acute and characteristic dermatitis, moderate glossitis, diarrhea, anorexia, indigestion, weakness, nervousness, or mental depression, without the severe prostration, fever, delirium, and grave prognosis of the more severe types.

Lastly, there are the so-called "formes frustes," which, according to Sydenstricker,[1058] are very common. This group of "pellagra fruste" comprises the very mild cases showing only one of the three D's and responding quite promptly to nicotinamide therapy. Katzenellenbogen[1059] includes in this group the stomatoglossitis seen among agricultural settlers in Palestine during the winter, when their diet is unbalanced.

Pellagra is an endemic disease, particularly in the southern United States, in the south of Europe, Egypt, and many other parts of the world. According to Spies and Butt,[424] pellagra is very common. Sebrell, of the United States Public Health Service, reports that in 1930 there were 1,037 deaths from this disease in North Carolina alone. The number of cases is considerably greater than published records would suggest, owing principally to the fact that many physicians are reluctant to consider this diagnosis unless the classic three D's are present; and this, as mentioned above, is the case only in advanced stages of the disease (Spies and Butt,[424] Stannus[377]).

It is now generally accepted that pellagra is caused by dietary deficiency, chiefly of the vitamin B complex, with a predominant lack of niacin. However, as we shall discuss below, other factors as yet poorly understood may also enter into the pathogenesis of this disease. In other words, pellagra is a disease of multiple causation rather than a manifestation of a specific nutritional deficiency.

It has been shown that certain typical phenomena of endemic pellagra, such as the seborrheic lesions, cheilosis, and scrotal dermatitis, are attributable to ariboflavinosis, while the neuritic symptoms are demonstrably due to thiamine deficiency, and the characteristic dermatitis, glossitis, and stomatitis are caused by a lack of niacin. Moreover, the dyssebacea will yield only to yeast and liver therapy, to some factors of the B complex other than those mentioned above.

The dietary deficiency may be due to various causes. In addition to the cases due to poverty, to alcoholism, and to prescribed or voluntary dietary restrictions, this disease will be encountered among the chronically insane inmates of mental hospitals, in institutions for the aged and infirm, and in individuals with gastrointestinal diseases, such as dysentery, gastric carcinoma, pyloric ulcer with short-circuiting operation, or rectal stric-

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1058. Sydenstricker, V. P.: Proc. 8th Amer. Scientific Congress. **6:** 65, 1940.
1059. Katzenellenbogen, I.: Lancet **1:** 1260, 1939.

ture, hepatic cirrhosis, diabetes, renal disease, hookworm disease, and others. To summarize, the most frequent cause of pellagra is failure to provide a balanced nutritional intake, resulting either from an inadequate diet or from factors interfering with the ingestion, assimilation, or proper utilization of food.

As already noted, pellagra is in all probability more than a simple deficiency disease. Thus, Sydenstricker and associates[1060] obtained improvement on administration of gastric juice and from this observation postulated a deficiency of the intrinsic factor of the stomach. Petri and co-workers[1060a] reported cures with ventriculin and hydrochloric acid. In their opinion, lack of this substance interferes with utilization of riboflavin in a manner analogous to that which is known to occur in pernicious anemia.

The introduction of niacin has revolutionized the treatment of pellagra. As suggested by Spies, therapy consists of 500 mg. of niacin or niacinamide daily, administered orally in divided doses. The peripheral vasodilation, particularly of the vessels of the face and neck, which generally follows from fifteen minutes to one hour after niacin has been taken and which is accompanied by flushing and a feeling of intense warmth, tingling, and itching in the affected skin, is less pronounced when the medication is given with meals. Since such vasomotor reaction is not caused by niacinamide, this substance is preferable to niacin, the antipellagric activity of both being the same. The initial therapeutic dose of 500 mg. daily should be continued for seven to ten days, after which it may generally be reduced to 100 mg. daily or even less, since the lesions of the skin, mucous membranes, and central nervous system will ordinarily have disappeared by this time. Supplementary medication should include thiamine 20 to 25 mg., riboflavin 5 mg., pyridoxine 50 mg. and all of the less well known members of the B complex in appropriate dosage. Vitamin A, ascorbic acid, and vitamin D should also be given. The patient should be kept on a broad general diet of high caloric value (3,000 to 4,000 calories) with particular attention to an adequate intake of meat, eggs, milk, and fresh vegetables.

3. Plummer-Vinson Syndrome

Another well established vitamin B deficiency disease is the syndrome described by Plummer and Vinson.[1061]

This condition, which is encountered almost exclusively in middle-aged women, presents a combination of hypochromic anemia with dysphagia

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1060. Sydenstricker, V. P., Armstrong, E. S., Derrick, C. J., and Kemp, P. S.: Am. J. M. Sc. 192: 1, 1936
1060a. Petri, S., Wanscher, O., Stubbeteglbjaerg, E. and Stubbeteglbjaerg, H. P.: Hospitalstid. 80: 817, 1937.
1061. Vinson, P. P.: Minnesota Med. 5: 107, 1922.

and glossitis. In the majority of cases, there is also achlorhydria. The lips are thin, and the opening of the mouth is small and inelastic, giving the patient a rather characteristic appearance. There are atrophic changes, most pronounced on the tongue, which becomes entirely smooth in typical cases; but there is associated atrophy in the mucosa of the mouth, pharynx, and esophagus. There are also signs of inflammation in that the lips may be swollen and crusted, and the tongue enlarged, tender, and bright red. Ahlbom[1062] and Anderson[1063] have noted that koilonychia ("spoon-shaped nails") is a common symptom. If the nails are not spoon-shaped, they may be soft and often break readily. Indeed, cheilosis or koilonychia may be the first symptom to call attention to the true nature of the disorder. As a rule, the erythrocytes number about 4,000,000 and are normal in size and shape, but the hemoglobin level is about 50 per cent (8.6 Gm.) and sometimes considerably lower; the fragility of the red blood cells is increased.

That this syndrome is a precancerosis has been established beyond any doubt by Ahlbom.[1062] In an analysis of 250 cases of carcinoma of the mouth and upper respiratory tract in women this author found that no less than 70 per cent had had the Plummer-Vinson syndrome. The dietary deficiency is probably in vitamin B. Treatment consists of iron and liver extract, the latter being far less effective alone than when given in combination with the former. Yeast and a liberal highly nutritious diet are also recommended.

In one of the present writer's own cases, medication with hydrochloric acid, pepsin, and pancreatin, plus iron, corrected the glossitis and anemia in a month. Broekema[1064] reports that the condition of the nails was found to respond favorably to treatment with liver extract and iron.

4. Miscellaneous Conditions Attributed to Vitamin B Deficiency

Morphologic changes in the tongue are sometimes the earliest manifestations of vitamin B deficiency disease. The tip or sides are usually the first parts to be affected, and changes are more commonly seen in the anterior than in the posterior half. In many cases the tongue is distinctly swollen, larger than normal, sometimes tender, and presents a red, glazed appearance which may be confined to a few small areas or may extend over a large portion of the dorsal surface. Superficial ulcerations, fissures, infiltrated patches, leukoplakia, and even papillomatous growth may develop. Aphthae are commonly present. In other cases the tongue has a smooth and atrophic appearance due to atrophy of the lingual papillae. Ulcers and/or diffuse keratotic changes may follow.

[1062] Ahlbom, H. E.: Brit. M. J. **2:** 331, 1936.
[1063] Anderson, N. P.: Arch. Dermat. & Syph. **37:** 816, 1938.
[1064] Broekema, J. H.: Acta dermato-venereol. **14:** 113, 1933.

The fact that administration of niacin, riboflavin, or of parenteral crude liver extract or simply brewers' yeast or vitamin B complex by mouth often leads to remarkable changes in these conditions of the tongue clearly indicates the true nature of their pathogenesis.

Andrews[1065] pointed out that leukoplakia, particularly those types which are associated with inflammatory conditions of the mucosa of the mouth, respond very well to niacin therapy. He suspects that the use of tobacco, like alcohol, is often the underlying cause of a deficiency state. He explains this by the fact that people frequently smoke instead of eating. Moreover, it is generally admitted that nicotine dulls the appetite for food. In this connection, it is interesting to note that Andrews,[1065] Gross,[225] and the present writer achieved encouraging results with vitamin B therapy in kraurosis vulvae. Rhoads[1066] and Swift[1039] described kraurosis vulvae in patients exhibiting the full or abortive picture of the Plummer-Vinson syndrome. Interesting and worthy of mention is Stryker and Halbeisen's[401] case who exhibited a diffuse squamous dermatitis (Fig. 216)

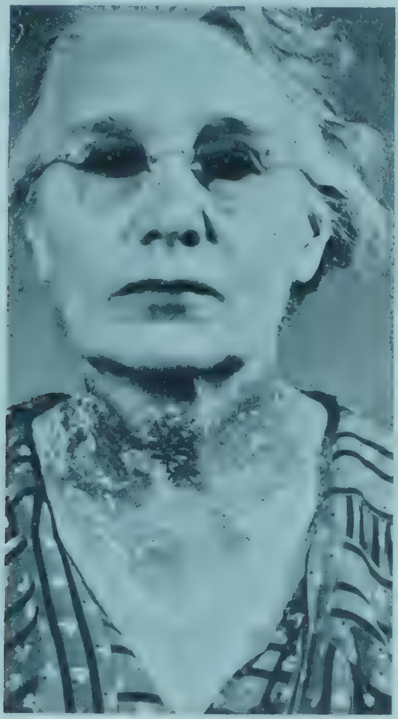

FIG. 216. DIFFUSE SQUAMOUS DERMATITIS OF THE NECK AND CHEST DUE TO VITAMIN B COMPLEX DEFICIENCY

The patient also exhibited macrocytic anemia. Both conditions were controlled by appropriate vitamin therapy.

(Courtesy of Dr. Stryker and the Archives of Dermatology and Syphilology.)

1065. ANDREWS, G. C.: Pennsylvania M. J. 43: 1535, 1940.
1066. RHOADS, C. P.: J. A. M. A. 113: 297, 1939.

associated with macrocytic anemia, both of which yielded to therapy with vitamin B complex.

Gross[225] reported a series of cases with extensive and localized seborrheic dermatitis which responded well to treatment with crude liver extract (Figs. 217, 218). He suggested that some of these might have been due to a secondary vitamin B complex deficiency, resulting from an underlying digestive or assimilative disorder. However, it is not claimed that liver therapy has a curative effect in the average case of seborrheic dermatitis.

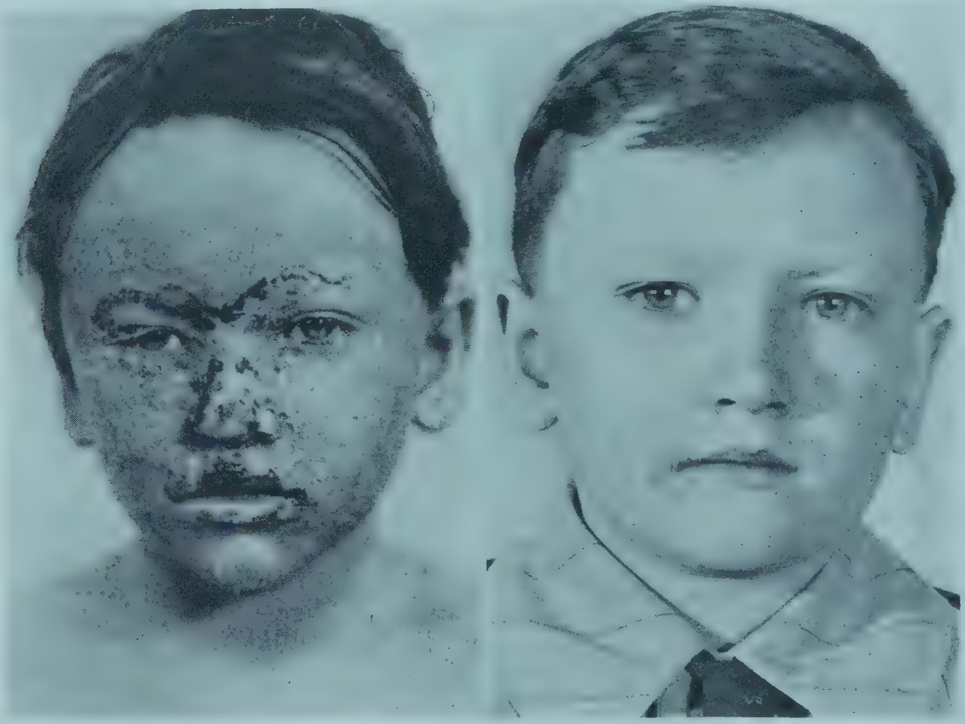

FIG. 217 FIG. 218

SEBORRHEIC DERMATITIS DUE TO VITAMIN B COMPLEX DEFICIENCY

FIG. 217. Before treatment.

FIG. 218. After three months of intensive therapy with crude liver.

(Courtesy of Dr. P. Gross and the Archives of Dermatology and Syphilology.)

Mashkilleison[405] saw disappearance of cutaneous manifestations in three cases of parapsoriasis guttata given 100 mg. niacin three times daily for some weeks.

According to Andrews[1065] and Gross[225] liver therapy is beneficial in extensive monilial infections of the skin. Gross explains that this kind of fungous infection occurs chiefly in diabetics, who, according to latest theories (see p. 167), suffer from vitamin B complex deficiency.

Lastly, mention should be made of Hollander's[1067] hypothesis that the papillary excrescences of acanthosis nigricans can be appreciably influenced by vitamin B complex therapy. Hollander regards this disease as a severe avitaminosis resulting from the patient's inability to consume and absorb the necessary vitamins, either because of the lack of gastric capacity, or because the digestive fluids are lacking in some essential components. This interpretation would explain the not uncommon occurrence of acanthosis nigricans in cachectic individuals suffering from carcinoma of the stomach or intestine, sarcoma, severe diabetes, or tuberculosis. Needless to say, the relatively good effect of vitamin B therapy on the cutaneous lesions does not delay or prevent death from the underlying malignancy.

[1067] HOLLANDER, L.: Arch. Dermat. & Syph. 48: 650, 1943.

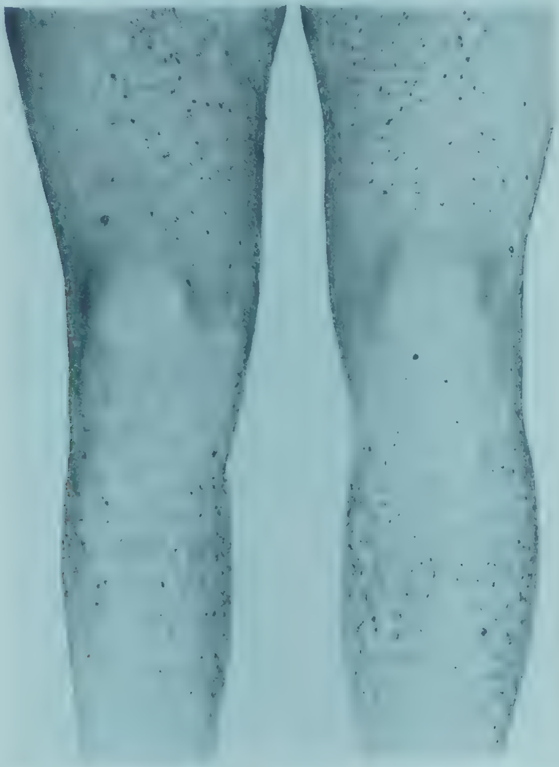

Fig. 219. Scurvy: Petechial Hemorrhages

C. SKIN DISEASES DUE TO VITAMIN C DEFICIENCY

The classic disease caused by deficiency in ascorbic acid is, of course, scurvy, the dermatologic aspects of which are fully discussed on page 190. The typical skin lesions consist of small purplish petechiae, from 1 to 3 mm. in diameter, grouped around the hair follicles on the thighs and legs (Fig. 219). These lesions may be associated with the appearances of bruises and deeper extravasations of blood (Fig. 220), as well as with the well known signs in the mouth (Figs. 221, 222) and the other symptoms mentioned above. Here also we wish to draw attention to follicular hyperkeratosis, which, according to recent investigations, is by no means pathognomonic of vitamin A deficiency (see p. 453). Nicolau,[494] dissenting, goes so far as to state that the follicular apparatus of the skin appears to be a sensitive index of even a slight deficiency in ascorbic acid. He reports, furthermore, that in the winter and early spring—that is, during the seasons when nutritional conditions are at their worst—he observed indigent Rumanian peasants who regularly developed keratotic papulofollicular manifestations and no other scorbutic symptoms. These lesions promptly yielded to medication with ascorbic acid (50 mg. daily). This observation was recently confirmed in cases of experimentally produced scurvy in man (Crandon and associates[493]). In this connection it is interesting to note that Chevalier and Civatte,[1068] as well as György,[1069] achieved marked improvement and sometimes even complete cure by giving patients with keratosis pilaris rubra (keratose pilaire rouge de grande intensité, Brocq) systematic injections of ascorbic acid. It may be well to mention a differential point emphasized by Machella,[1070] namely, that until the red perifollicular areolae or perifollicular hemorrhages develop in advanced scurvy, it is impossible to distinguish between such lesions appearing in vitamin A deficiency and those characteristic of ascorbic acid deficiency. Determination of the ascorbic acid level of the blood and performance of the Rumpel-Leede test (Fig. 223) will be helpful in differentiating between these conditions.

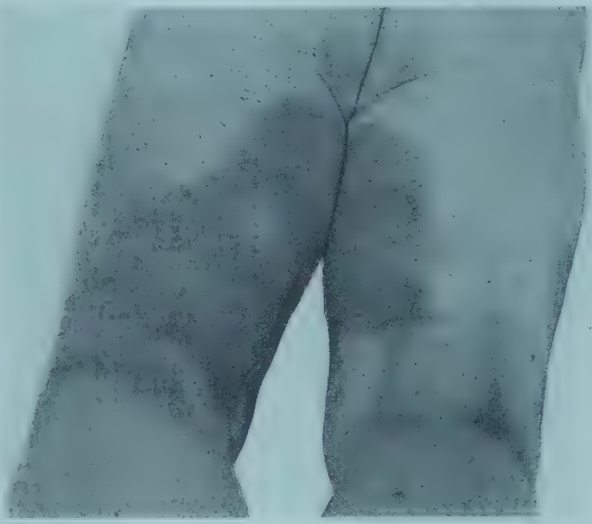

FIG. 220. SCURVY: EXTENSIVE EXTRAVASATIONS

Andrews stresses[1065] the point that subclinical cases of scurvy are fairly

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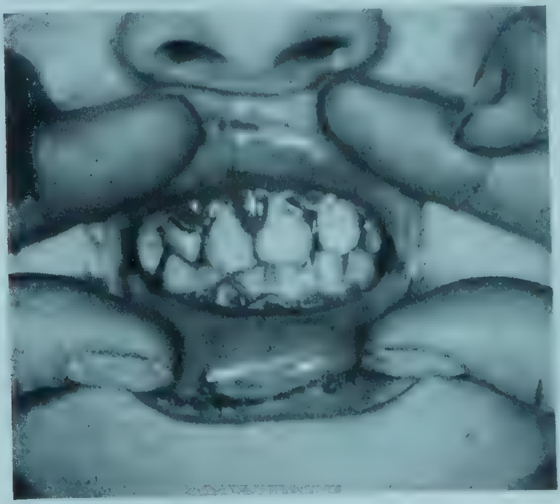
[1068] CHEVALIER, P. and CIVATTE, A.: Bull. Soc. franc. de dermat. et syph. 43: 760, 1936.
[1069] GYÖRGY, P.: Arch. f. Dermat. u. Syph. 17: 706, 1937.
[1070] MACHELLA, T. E.: Pennsylvania M. J. 45: 941, 1942.



Oral Manifestations of Scurvy

Fig. 221. Spongy, bleeding gums.

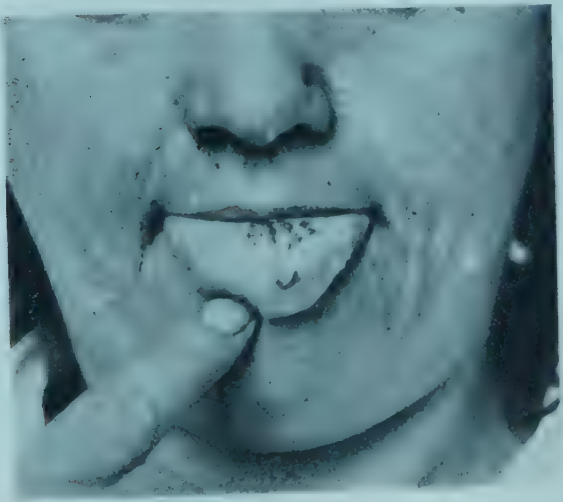


Fig. 222. Hemorrhagic lesions of the tongue.

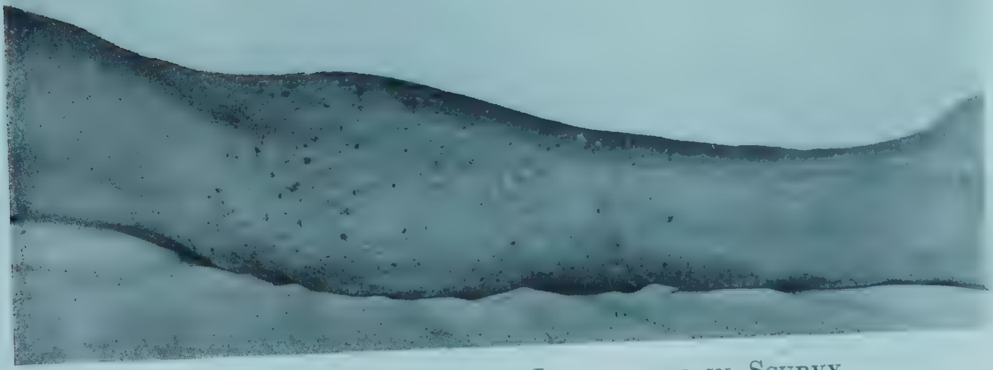


Fig. 223. Positive Rumpel-Leede test in Scurvy

common and of importance to the dermatologist in that they heighten the hemorrhagic characteristics of such eruptions as the patients may have. He noticed this chiefly in cases of erythema multiforme and in drug eruptions, but it is difficult to prove this point conclusively.

Of special dermatologic interest is the question as to whether ascorbic acid is capable of reducing susceptibility to sensitization, as postulated by Sulzberger and Oser.[512] Since the current opinions on this question were considered in some detail on page 194, there is no need for further discussion at this point. On page 192 the reader will also find a short résumé of the relationship between ascorbic acid and pigment metabolism. Here we shall merely call attention to the fact that pigmentary disturbances are commonly seen in scurvy and that they disappear under treatment with ascorbic acid (Cornbleet,[499] Goldsmith[1071]). Hemosiderin is responsible for the brownish discoloration in scurvy, but the diffuse pigmentation seen in occasional cases suggests overproduction of melanin as well (Goldsmith[1071]).

1071. Goldsmith, W. N.: Recent Advances in Dermatology. Philadelphia: Blakiston, 1936.

CHAPTER XII

Diseases of Sebaceous and Sudoriferous Glands

A. ACNE VULGARIS

ACNE vulgaris is a chronic inflammatory disease of the sebaceous glands and the pilosebaceous structures of the skin and is almost always associated with seborrhea. This cutaneous condition is by no means due to any one cause; quite commonly it arises as a result of the cumulative effect of a number of factors. From the etiologic viewpoint, patients with acne can be subdivided into six distinct groups: endocrine, gastrointestinal, infectious, allergic, nutritional, and medicamentous. However, as mentioned above, none of these need necessarily appear as a separate entity in a given case, two or more factors sometimes being combined. The success of treatment therefore depends to a great extent on determination of the pathogenesis.

Endocrine acne. Most common of the various forms of acne is unquestionably that of endocrine origin. Among 330 youths in the 15 to 18 year age group, the writer[1072] noted pronounced acne in 13 per cent of the boys of 15, in 14 per cent of the boys of 16, in 20 per cent of those of 17, and in 25 per cent of the boys of 18. Indeed, when mild cases are taken into consideration, it may be said that some 67 per cent of all adolescents show some degree of acne (Bloch,[822] Hinrichsen and Ivy[1073]). Nothing can be done about eliminating this etiology in acne, at least at the present time. This is not the case, however, when the cutaneous manifestations are markedly exacerbated before menstruation. Leszczynski and Liebhardt[1074] have demonstrated that appropriate endocrine therapy adapted to the particular type of menstrual disturbance often brings relief. These authors found that, depending upon the endocrine disturbance, administration of follicular, corpus luteum, or pituitary hormones was useful; in some cases x-ray therapy of the hypophysis was of value, while in others thyroid medication was beneficial.

Rosenthal[1075] and others have reported satisfactory results in the treatment of acne with injections of gonadotropic substance extracted from the urine of pregnant women. In cases showing greatly reduced or totally absent estrogen excretion in the urine, Urbach and Schiller[1076] obtained notable improvement by administering estrogenic substance for three consecutive months (10,000 rat units every third day from the sixth to the eighteenth day after menstruation) plus progestin (2.5 mg. daily from the nineteenth to the twenty-second day). Before incurring the expense of hormonal treatment, the present writer[1077] always tries therapy with autogenous premenstrual serum in patients who show a flare-up of the lesions before menstruation. The blood for this purpose is obtained premenstrually just as soon as an exacerbation of the acne occurs. During the intermenstrual intervals, the patient is given a course of 9 to 11 intracutaneous injections (each of 0.2 cc. of autogenous serum), administered every other day, four times in the same skin site and the next four times in another skin site.

[1072] Urbach, E.: Dermat. Ztschr. **54:** 92, 1928.

[1073] Hinrichsen, J. and Ivy, A. C.: Arch. Dermat. & Syph. **37:** 975, 1938.

[1074] v. Leszczynski, R. and Liebhardt, S.: Dermat. Ztschr. **94:** 261, 1932.

[1075] Rosenthal, T.: M. Clin. North Amer. **20:** 985, 1936.

Hollander,[1078] Covisa and Bejarano,[1079] Leszczynski and Liebhardt,[1074] and others are of the opinion that especially severe acne eruptions on the face and trunk which are associated with very pronounced seborrhea oleosa are due to hyperfunction of the thyroid gland. They claim to have observed marked improvement following appropriate treatment, particularly x-ray radiation of the thyroid gland.

Gastrointestinal acne. There can be no doubt that in many cases gastrointestinal disturbances play a major etiologic role. On the basis of gastric analysis and roentgenologic examination, Ketron and King[1080] state that acne is often accompanied by disturbances of the gastrointestinal tract. Knowles and Decker[1081] quite frequently encountered subnormal gastric acidity in their patients and noted improvement following administration of hydrochloric acid. These observations have been confirmed by Stokes and Sternberg.[1082] However, Huebschmann[1083] reported a case of acne which did not yield to therapy until gastric hyperacidity had been controlled. Also, Immerman[1084] found no apparent correlation between acne and gastric acidity in 93 cases. Having demonstrated hyperindicanemia in quite a number of instances, Hermans and Belinfante[1085] are inclined to regard putrefactive processes in the intestine as a cause of acne. According to Friedenwald and Morrison,[735] intestinal diseases, particularly those of an inflammatory nature (e.g., colitis), as well as fermentation, putrefaction and constipation, are capable of giving rise to

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1076. Urbach, E. and Schiller, W.: Med. Klin. **33:** 1701, 1937.
1077. Urbach, E.: Internat. Clin. **2:** 160, 1939.
1078. Hollander, L.: Arch. Dermat. & Syph. **3:** 593, 1921.
1079. Covisa and Bejarano: Acta dermo-sif. **16:** 161, 1924.
1080. Ketron, L. W. and King, J. H.: Dermat. Wchnschr. **65:** 1048, 1917.
1081. Knowles, F. C. and Decker, H. B.: Arch. Dermat. & Syph. **13:** 215, 1926.
1082. Stokes, J. H. and Sternberg, T. H.: Arch. Dermat. & Syph. **40:** 345, 1939.
1083. Huebschmann, K.: Cěská Dermat. **1:** 128, 1920.
1084. Immerman, S. L.: Arch. Dermat. & Syph. **31:** 343, 1935.
1085. Hermans, E. H. and Belinfante, A. J. G.: Neederl. tijdschr. v. geneesk. **74:** 1316, 1930.

acne, probably through the irritative action of the toxins on the pilosebaceous apparatus. Appropriate dietary measures, management of the pathologic fermentation or putrefaction, regulation of bowel movements, and correction of pathologic intestinal flora as described in some detail on page 320, can often lead to surprisingly rapid improvement and permanent cure. According to Leszczynski and Liebhardt,[1074] intestinal acne is characterized by a greater tendency to involve the trunk. Mention must also be made here of the importance of eliminating intestinal parasites.

Infectious acne. Positive animal inoculation experiments with acne pus, together with the apparent resemblance (particularly of acne indurata) to the colliquative type of tuberculosis, as well as the finding of tubercle bacilli in the urine in a series of patients, led Ramel[1086] to believe that this form of acne is fundamentally of tuberculous origin. The present writer found that cases belonging to this clinical group not infrequently showed a pronounced reactivity to small doses of old tuberculin—e.g., 0.1 cc. of a 1:1,000,000 dilution. And van Studdiford[1087] reported improvement on treatment with tuberculin. Moreover, a tuberculous origin is suggested in certain cases of acne conglobata and indurata by the good results obtained by Oppenheim[1088] with the Gerson diet. Lerner[1089] observed good response to a diet in which table salt was equilibrated by Cationorm, a preparation made up of calcium, potassium, and magnesium which, according to Keining and Hopf,[81] may be used instead of a salt-free diet (see p. 70).

This group also properly includes all those cases which are apparently the result of focal infection (in teeth, tonsils, sinuses, gallbladder, appendix, renal pelvis), for eradication of the focus of infection sometimes leads to marked improvement in the cutaneous eruption. The question as to whether the irritation of the pilosebaceous apparatus involved here is infectious or toxic cannot be answered with any degree of assurance.

Allergic acne. Work done in this field during the past few years has served to establish the fact that in a small percentage of cases the acne is due to an underlying food allergy. Thus, Rowe,[25] White,[1090] Cunningham and Mendenhall,[1091] Cormia,[1092] Stokes and Sternberg,[1082] and others have described a number of cases with food hypersensitiveness determined by elimination diet, severe exacerbation on administration of incriminated foods, and marked improvement following withdrawal of these aliments. The chief offenders were found to be chocolate, milk, wheat, oranges, toma-

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1086. Ramel, E.: Schweiz. med. Wchnschr. **60:** 754, 1930.
1087. Van Studdiford, M. T.: Arch. Dermat. & Syph. **38:** 737, 1938.
1088. Oppenheim, M.: Zentralbl. f. Haut- u. Geschlechtskr. **54:** 482, 1937.
1089. Lerner, C.: Arch. Dermat. & Syph. **31:** 526, 1935.
1090. White, C.: J. A. M. A. **103:** 1277, 1934.
1091. Cunningham, T. D. and Mendenhall, J. C.: J. Allergy **7:** 378, 1936.
1092. Cormia, F. E.: J. Allergy **12:** 34, 1940.

toes, spinach, and nuts. Figure 224 shows a case of the present writer's in which tomato hypersensitiveness was established as the chief cause of acne. Moreover, an interesting and conclusively proven case of hypersensitiveness to yeast was described by Stokes.[1082] In cases of this kind, skin tests are of no value, but the responsible food or foods can readily be identified by means of the elimination diet (p. 243) or the Propeptan diet (p. 251).

Sulzberger and co-workers[1093] incriminate not so much the protein or carbohydrate factors in foods as the traces of chemicals contained in them, such as iodine and bromide, which, in their opinion, may irritate the pilosebaceous apparatus. Thus, they consider the process affecting the sebaceous glands to be toxic rather than allergic. As is well known, such food items as seafood, spinach, cabbage, and artichokes have a high iodine content. Moreover, as mentioned on page 210, vegetables and fruits grown in places where certain chemical fertilizers are used may contain as much as one hundred times more iodine than those grown with animal fertilizers. Furthermore, as Shelmire,[1094] Bechet,[1095] and others have shown, the minute quantities of iodine in iodized salt suffice to cause exacerbations of acne in some individuals. In fact, severe ioderma may be induced in this manner. In this connection, it is interesting to note that Sulzberger[1093] and Cormia[1092] do not consider the aggravation of this condition, which sometimes occurs after ingestion of white bread, to be evidence of specific food hypersensitiveness; they believe that such exacer-

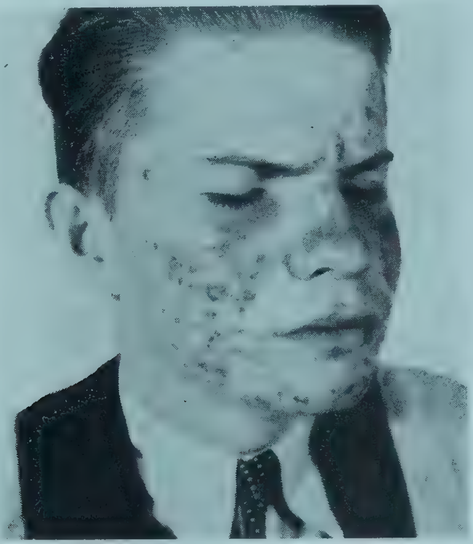

FIG. 224. ACNE VULGARIS DUE TO TOMATO HYPERSENSITIVENESS

1093. SULZBERGER, M. B., ROSTENBERG, A. JR., and SHER, J. J.: New York State J. Med. **34:** 899, 1934.
1094. SHELMIRE, B.: J. A. M. A. **90:** 1869, 1928.
1095. BECHET, P. E.: Arch. Dermat. & Syph. **29:** 529, 1934.

bations are attributable to the baking "improvers" in the bread, explaining that they contain potassium bromate which is reduced to bromide in the process of baking. Thus, the favorable response to an elimination diet cannot always be interpreted as conclusive proof of a nutritional allergy or as an indication that the acne is due to the large quantities of carbohydrates in white bread. In any event, acne patients should avoid iodides and bromides in their frank form, as in iodine medication, cough medicines, bromide sedatives, tonics, and laxatives. Even the liberal use of ordinary table salt (derived from sea water) may be noxious, since it contains as much as 10 parts of bromine per 100,000. Figure 225 is representative of acne due to iodide allergy.

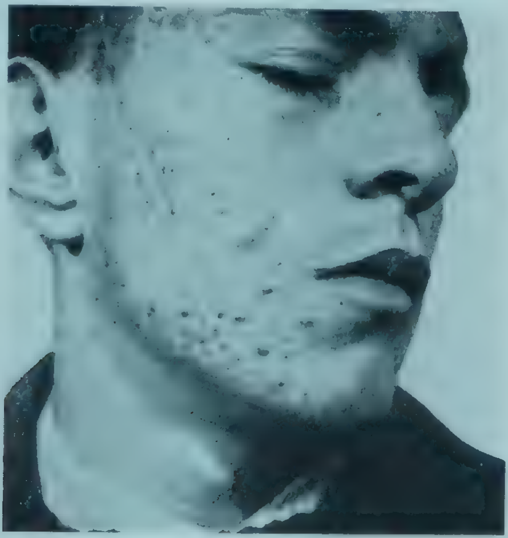

FIG. 225. ACNE VULGARIS DUE TO IODIDE ALLERGY

Nutritional acne. Lastly, there is a large group of acne cases in which none of the above-mentioned causes can be demonstrated but in which the condition is nevertheless obviously related in some way to the patient's diet. The great question that has for years dominated the study of the pathogenesis of acne concerns the significance of the diet in the production and therapy of this condition. Opinions vary considerably, running the gamut from the view that dietary factors play no role whatever to the extreme opposite view of those who consider the diet to be the most important factor in the causation and management of acne.

A critical glance at the voluminous but contradictory literature on the subject of dietary therapy in acne must lead to the conclusion that this condition can hardly be expected to yield to nutritional measures alone. In the present state of our knowledge, we cannot unequivocally answer the fundamental question as to whether a diet high in fat is more harmful to acne patients, or, more properly, seborrheic individuals, than one high in carbohydrates. According to the findings of Rosenfeld,[1096] Kuznitzky,[1097] and Birk[1098] the secretion of sebum is greater on a high carbohydrate than on a high fat diet.

The common clinical experience that gross dietary indiscretion, particularly in the form of overindulgence in cakes, candy, ice cream, and chocolate, aggravates an existing acne strongly suggests that the skin condition may be associated with a disturbance of the carbohydrate metabolism. Indeed, earlier reports seem to indicate the presence of at least a borderline hyperglycemia in an appreciable percentage of acne patients (Schwartz,[1099] McGlasson[1100]). Menagh and co-workers[1101] found that no less than 70 per cent of their acne vulgaris cases exhibited a diminished tolerance for glucose, and they obtained better results when this group was treated with insulin and desiccated thyroid. Semon and Herrmann[1102] demonstrated that women with premenstrual flare-ups of acne often show a pathologic blood sugar tolerance curve. These authors reported that 8 units of protamine-zinc insulin, given twice weekly plus additional doses every other day immediately before and during menstruation, led to marked improvement without local treatment. However, it is difficult to say whether this points to a disturbance of the sugar metabolism or suggests the possibility of an additional relationship between hormonal abnormalities and the skin, notably the sebaceous glands. Schamberg,[1103] Strickler,[1104] and their co-workers found normal blood sugar levels in their acne patients; and Crawford and Swartz[1105] even reported definite improvement in cases receiving a high carbohydrate diet. On the strength of their findings, the latter authors doubt that persons suffering from acne are intolerant of carbohydrates. However, there may be a relationship between a high carbohydrate diet and acne without invoking the assumption of a disturbance of the sugar metabolism. Thus, according to Gross,[840] the danger inherent in an excessive carbohydrate intake lies in the well established fact that both sugar and refined flour are seriously lacking in vitamins. Naturally, a high proportion of such carbohydrates in the diet will tend to reduce the intake of the unrefined cereals, with their vitamin B complex. To make matters worse, an increase of carbohydrates in the diet actually raises the requirements for vitamins, especially those

1096. Rosenfeld, G.: Zentralbl. f. inn. Med. **40:** 986, 1906.
1097. Kuznitzky, E.: Arch. f. Dermat. u. Syph. **114:** 691, 1913.
1098. Birk, W.: Monatschr. f. Kinderh. **8:** 394, 1909.
1099. Schwartz, H. J.: J. Cut. Dis. **34:** 159, 1916.
1100. McGlasson, I. L.: Arch. Dermat. & Syph. **8:** 665,1923.
1101. Menagh, F. R., Foster, D. P., and Reyner, C. E.: J. Michigan Med. Soc. **37:** 521, 1938.
1102. Semon, H. C. and Herrmann, F.: Brit. J. Dermat. **52:** 123, 1940.
1103. Schamberg, J. F. and Brown, H.: Arch. Dermat. & Syph. **21:** 1, 1930.
1104. Strickler, A. and Adams, P. D.: Arch. Dermat. & Syph. **26:** 1, 1932.
1105. Crawford, G. M. and Swartz, J. H.: Arch. Dermat. & Syph. **33:** 1035, 1936.

of the water-soluble group. Still another viewpoint was expressed by Stokes and Sternberg,[1082] who are of the opinion that hydration of the tissues is a factor directly predisposing to infection, including involvement of the pilosebaceous apparatus. These authors feel, therefore, that the cutaneous hydration associated with menstruation may be the explanation of the menstrual flare of acne, and that carbohydrates, acting as cutaneous hydrating agents, may thus have an unfavorable influence on acne in general and on menstrual acne in particular.

Sutton, Jr.,[921, 256] has for several years championed the theory that acne vulgaris is an epidermal pustular lipoidosis attributable to an imbalance between the dietary intake of lipoids and/or lipochrome substances and the patient's capacity to metabolize them. He postulates a disturbance in the lipoid metabolism analogous to the abnormal carbohydrate metabolism in diabetes mellitus and claims that it can be controlled by restricting the intake of fat. Moreover, he is of the opinion that the condition is generally accompanied by a moderate degree of hypothyroidism, resulting, in some instances, from the thyroxin-inhibiting effects of the excessive amounts of vitamin A administered when adolescents are overloaded with cod liver oil and vitamin A concentrates.

Sutton, Jr., attempts to control this imbalance by: (1) a low fat diet; (2) administration of thyroid substance which tends to lower the blood cholesterol level; and (3) the mechanical evacuation of lipoid deposits from the comedones. According to this author, the total caloric intake is not to be curtailed but is to be obtained from carbohydrates and not from fats. His diet, therefore, consists of cereals, fruits, and vegetables (except nuts, chocolate, and vegetable cooking oils), sugar, salt, pepper, spices, flavorings, and lean meat in rather small quantities. Foods not permitted are: milk, cream, ice cream, butter, butter substitutes, cheese, lard, Crisco, cooking oils, shortened foods, fried foods, pork, ham, bacon, sausage, chocolate and cocoa, nuts and peanut butter, cod liver oil, vitamin A concentrates, cream soup, gravies, catfish, Spanish mackerel, smoked herring, shad, canned fish, salmon, tuna, sardines, mutton, brains, yolk of egg, and oatmeal.

For rosacea-like forms of acne, Sutton, Jr., recommends a diet low in carotenoids, avoiding carrots, pumpkin, sweet potato, spinach, tomato juice, catsup, and beets. Two oranges are permitted per day. In addition, the patient may take colorless or lightly colored vegetables and fruits, such as beans, peas, corn, grapefruit, pears, apples and bananas. In order to maintain normal thyroid function, iodized salt may be used in cooking. In pregnancy, calcium must be added, since the diet is low in this mineral. Sutton, Jr., states that this dietary is intentionally low in vitamin A but may be continued with impunity for a period of six months.

Moreover, he stresses the importance of adhering to it strictly and uninterruptedly.

Sutton, Jr., further suggests that all cases be given thyroid substance in doses up to the threshold of tolerance, regardless of the basal metabolic rate or the blood chemistry. He gives 2 grains of desiccated whole gland substance daily with the evening meal routinely. The optimum dose must be determined by clinical trial for each case and should be just short of the amount that will provoke the first signs of an untoward reaction.

While the opinion is widely held that acne is exacerbated by fat, the value of a low fat diet and particularly the concept of acne vulgaris as an epidermal lipoidosis are still highly controversial questions. It cannot be denied, however, that many dermatologists have seen acne make its appearance following attempts at pushing fatty foods such as milk, cream, butter, and chocolate, especially in girls who are trying to gain weight, or following overindulgence in ice cream in the summer. Bulkley[1106] points to bananas and nuts as having a notoriously unfavorable influence on acne. According to Wills,[1107] it is generally believed in the West Indies that bananas are responsible for acne in children whose diet consists largely of this fruit. Bommer[195] regards lard, bacon, margarine, and tallow as common causal factors. Wills[1107] recalls that it is well known among sailors that the salt pork diet at sea—in other words, pork fat—is likely to produce pustular acne. He believes that this is due to the fact that the melting point of this fat differs from that of the ordinary sebaceous oil; as a result of this difference, Wills reasons, the sebum in individuals on such a diet remains in the follicles as fatty plugs which provide a rich medium for bacterial growth and consequent deleterious effects on the sebaceous glands.

Montgomery and Culver[1108] insist that the intake of fat, as well as of cheese, be restricted. The latter, according to Buschke and Fraenkel[1109] definitely exacerbates the condition of many acne patients. Brocq[274] recommends complete avoidance of fat and alcoholic beverages for a whole year. It is Sutton's[921] opinion that administration of excessive quantities of cod liver oil to adolescents (e.g., in children's homes) causes the formation of comedones and promotes acne. Buchanan et al.,[912] Whitfield,[1111] Wright,[970] and others consider a low fat diet to be a valuable adjuvant in the treatment of this disease.

From this brief survey of the literature it can be seen that many authorities classify animal and vegetable fats as potential causes of acne. But the concept of this condition as an epidermal lipoidosis—i.e., an expression of a disturbance of the fat metabolism in the skin—is challenged by the following facts. LeWinn and Zugerman[1112] made a study of the fat tolerance, as indicated by blood cholesterol changes from ninety minutes to seven and one-half hours following the ingestion of fat, in a group of acne patients. They found that the latter in no way differed from a group of normal controls in this respect. Nor were Strickler and Adams[99] able to demonstrate any departure from the normal in the fasting blood cholesterol levels of acne patients. Moreover, as Corcoran and Rabinowitch[1113] pointed out, the diet of the Eskimo consists essentially of fat and protein, but not a single case of acne was observed among fifteen hundred Eskimos. It is to be noted, furthermore, that these people consume no less than 50,000 international units of vitamin A daily.

[1106] Bulkley, D.: On the Relations of Diseases of the Skin to Internal Disorders. New York: Rebman, 1906.

[1107] Wills, W. K.: Practitioner **128:** 331, 1932.

[1108] Montgomery, D. W. and Culver, S. D.: J. Cut. Dis. **30:** 523, 1912.

[1109] Buschke, A. and Fraenkel, A.: Berl. klin. Wchnschr. **42:** 318, 1905.

[1111] Whitfield, A.: Brit. J. Dermat. **46:** 257, 1934.

Opinions are also sharply divided as to the true therapeutic value of the various vitamins. On the assumption that the basic primary lesion in acne is a manifestation of hyperkeratosis of the pilosebaceous follicle identical with the hyperkeratosis described in vitamin A deficiency, Straumfjord[1043b] treated one hundred acne patients with a supplement of 100,000 I.U. of vitamin A daily for six months, and claimed that the eruptions disappeared completely in seventy-nine of these cases. Maynard[1115] also noted a gratifying response to treatment with vitamin A. Obermayer and Frost[1043] found vitamin A to be beneficial only in those forms which are characterized by marked follicular plugging in addition to the formation of comedos, that is, in a category which comprises only a small fraction of all acne cases. On the other hand, Sutton, Jr.,[1116] found that vitamin A concentrate aggravates the condition because, in his opinion, it is antagonistic to thyroxine, which is diminished in acne as a result of an accompanying hypothyroidism. Callaway et al.,[1117] however, could not demonstrate any abnormality in the vitamin A or carotene blood levels in patients with acne.

Vitamin D has been endorsed by Doctorsky[1118] and Hinricksen and coworkers,[1119] who noted particularly favorable results when large doses (100,000 U.S.P. units for four to eight weeks) were used. However, Wright[970] found that the improvement continued only so long as the patient was taking the vitamin and states that lasting cures cannot be

[1112] LeWinn, E. B. and Zugerman, I.: J. Lab. & Clin. Med. **28:** 190, 1942.

[1113] Corcoran, A. C. and Rabinowitch, I. M.: Biochem. J. **31:** 343, 1937.

[1115] Maynard, M. T. R.: Arch. Dermat. & Syph. **41:** 842, 1940.

[1116] Sutton, R. L. Jr.: J. Missouri M. A. **38:** 50, 1941.

[1117] Callaway, J. L., Milan, D. F., and Noojin, R. O.: Arch. Dermat. & Syph. **51:** 266, 1945.

[1118] Doktorsky, A. and Platt, S. S.: J. A. M. A. **101:** 275, 1933.

[1119] Hinrichsen, J. and Ivy, A. C.: Illinois M. J. **74:** 85, 1938.

achieved by this method. Simpson and associates[1120] pointed out that the larger the series, the less encouraging the results seemed to be.

Sutton, Sr.,[841] reported gratifying results with a liver diet in cases presenting deep-seated acne nodules; and Stokes[1082] and Smith and co-workers[1057a] found that cases of this kind yielded to treatment with yeast extract of a high potency, liver extract, and, above all, pyridoxine. The beneficial action of the latter was confirmed by Jolliffe et al.,[459] who administered from 50 to 250 mg. of pyridoxine orally daily, in divided doses.

TABLE 83.—*Diet in Acne Vulgaris*

Purpose of the diet: To restrict the intake of foods or drugs which clinical experience has shown to be capable of provoking exacerbations of acne vulgaris.

The following foods are prohibited:

Fried foods
Cheeses, except cottage or cream cheese
Alcoholic drinks
Soda fountain drinks
Ice cream
Chocolate
Pastries
Pies
Cakes
Oils and oily salad dressing
Nuts
Jams
Jellies
Marmalades
Preserves
Honey
Syrups of canned foods

Foods or drugs containing iodides or bromides, such as iodized salt, Bromoquinine, Bromo-seltzer, and similar preparations

The following foods are permitted in limited quantities:

Fats
Egg yolk
Cream
Potatoes
Bread
Rice
Noodles
Macaroni
Spaghetti
Sugar
Sherbets
Condiments

The following foods are allowed without restriction:

Lean meats, fish, fowl
Whole grain cereals and their preparations (bread, crackers, rolls, muffins)
Cooked or raw vegetables
Fresh or stewed fruits, fruit juices
White of egg
Cottage or cream cheese
Skimmed milk
Buttermilk
Weak tea
Weak coffee

Medicamentous acne. In addition to iodine and bromine compounds taken internally, the chlorine vapors to which factory and laboratory workers are so frequently exposed are capable of causing acne.

1120. SIMPSON, C. A., ELLIS, F. A., and KIRBY-SMITH, H.: Arch. Dermat. & Syph. 41: 835, 1940.

Aside from the six major etiologic types of acne there are, as Stokes and Sternberg[1082] have stressed, other factors which should always be taken into consideration from the therapeutic viewpoint. For one thing, there can be no doubt that the psychoneurogenous factor often plays a major role in eliciting an exacerbation. The present writer has quite frequently been able to trace a new outbreak to nervous tension incident to final examinations at school, to physical and mental strain in student nurses during their first semester of hospital training, and not uncommonly to emotional disturbances of romantic or social origin. Moreover, fatigue and exhaustion are often overlooked as important predisposing factors. Plenty of good, restful sleep is absolutely essential here. Furthermore, the physician should always search for and deal with any seborrheic processes, notably in the scalp.

TABLE 84.—*Sample Menu for Acne Vulgaris*

Breakfast:	Cooked or prepared whole grain cereal with milk Whole grain toast or roll with cream cheese Skimmed milk
Luncheon:	One egg, any style except fried, *or* cottage cheese Cooked vegetables Salad with lemon juice Whole grain crackers Fresh or stewed fruit Skimmed milk
Dinner:	Fruit juice or vegetable juice Lean meat, or fish or fowl Cooked vegetables, other than potatoes Salad with lemon juice Whole grain bread Sherbet Skimmed milk

The present writer has found the following dietary regimen to be helpful in the management of acne (Tables 83, 84).

Finally, we should like to call attention to a fault very frequently encountered in young people with acne, that is, rapid eating and improper mastication.

In addition to dietary measures menstrual irregularities, endocrine disturbances, constipation, anemia, psychosomatic influences, fatigue, general or focal infections, food and drug allergies must be corrected. Lastly, local treatment is absolutely indispensable. We begin this therapy with a steam bath of the face, in which the face is exposed from all sides to very hot steam and then washed with very cold water. The comedos are then quite readily expressed by means of a suitable comedo squeezer. Inflamed comedos must be opened with a very small bistoury. X-ray treatment is advisable in cases with marked seborrhea of the face. Seborrhea of the scalp should be treated with sulfur preparations incorporated in greaseless bases such as Pragmatar or Collo-Sul.

B. SEBORRHEA

Seborrhea is a functional disorder of the sebaceous glands characterized by an increase in the amount of sebum secreted, and probably also by qualitative changes (Fig. 226). Thus, under normal conditions the ratio of cholesterol esters to free cholesterol is 2:1, while in seborrhea the esters are relatively increased (Marchionini et al.[1122]).

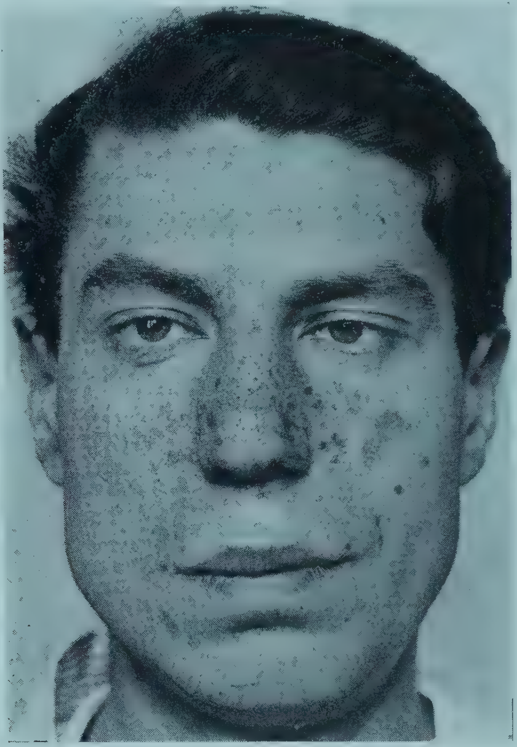

FIG. 226. SEBORRHEA OLEOSA

Seborrhea often leads to inflammatory processes which are known as seborrheic dermatitis and are described in detail on page 403. Here we are concerned only with those conditions which are clinically noninflammatory.

Except for the form which makes its appearance in infancy, seborrhea occurs most frequently at puberty or during adolescence, that is to say, at the time of the greatest gonadal activity. However, this does not necessarily warrant the conclusion that seborrhea is chiefly due to endocrine factors. While the pathogenesis of this disorder is so far not well understood, experimental results, including a number of investigations carried out many years ago, clearly indicate that the nature of the diet has a direct bearing on the oiliness of the skin in this condition. The concept that the carbohydrate intake influences the secretion of fat by the skin, and hence the seborrheic group of dermatoses, is supported by Rosenfeld's[1096] findings. By extracting the daily output of sebaceous secretion absorbed by clean woolen underwear, he showed that greater amounts of oily matter are secreted on a high carbohydrate than on a high fat diet. This was confirmed by Kuznitsky[1097] and Birk.[1098] On the other hand, Somekawa[1123] produced unequivocal seborrhea of the skin of rats by feeding the animals a diet containing from 10 to 15 per cent of natural whale oil

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[1122] MARCHIONINI, A., MANZ, E. and HUSS, F.: Arch. f. Dermat. u. Syph. **176**: 613, 1938.

It is clinical observation, however, which most strongly suggests that the composition of the oily secretion of the skin can be influenced by the diet. Thus, Sutton and Sutton[337] insist that excessive intake of fat, of concentrated carbohydrate foods, or of alcohol is instrumental in causing and aggravating seborrhea. According to Barber,[179] the sebaceous glands not only produce sebum by a process of true secretion (adipogenesis), but can also fix excessive quantities of circulating fat (adipopexy). (For more detailed discussion of this question see page 92). In all probability, the adipopexic function of the sebaceous glands is responsible for the change in the composition of the sebum. Montgomery[257] pointed out that when the diet contains excessive amounts of fat, especially of butter fat, the sebaceous glands secrete fatty substances which are particularly susceptible to bacterial decomposition, whereas under ordinary conditions they produce a fatty substance which is fairly resistant to bacterial action. This, of course, renders the patient susceptible to acne and furuncles. The theory that the chemical composition of the sebum is influenced by the adipopexic function of the sebaceous glands and that the altered sebum encourages the active growth of the saprophytes of the skin (Pityrosporum, Corynebacterium acnes, Staphylococci) would explain Wills'[1107] observation that some cases of severe seborrheic acne yield to the omission of pork fat from the diet, as well as of Buschke's[1109] and other authors' findings that in certain patients cheese will invariably provoke an outbreak of the eruption.

Aside from the question of fats, it seems likely that, when taken in excessive quantities, carbohydrates tend to aggravate seborrhea. Barber[1124] calls attention to the fact that concentrated sweets and soft starchy foods

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1123. Somekawa, E.: Sc. Papers, Inst. Phys. & Chem. Research, Tokyo **12:** 149, 1933.
1124. Barber, H. W.: Lancet **2:** 363, 1929.

which cannot be properly masticated, and particularly when cooked with milk, tend to ferment with the production of fatty acids and gas. Sabouraud[1125] emphasized the spectacular results sometimes achieved merely by excluding bread from the diet of obese seborrheic individuals, many of whom habitually consume large quantities of this food stuff with their meals.

Seborrhea oleosa may be caused by dietary excess of fats or carbohydrates, but the fault may also sometimes lie in inadequacy of the metabolic processes rather than in their being overloaded. Thus, according to Sutton and Sutton,[337] hypothyroidism may be a causal factor, and a trial with thyroid substance is therefore suggested by them. More recently, Jolliffe and associates[459] have demonstrated that pyridoxine (50 to 250 mg. daily, in divided doses) definitely reduces the oiliness of the skin. It seems that chemical processes which increase oxidation have a beneficial influence on the seborrheic state.

Moreover, the experimental work of Perutz and co-workers[1126] has revealed that the mid-brain contains an inhibitory center whose destruction is followed by excessive excretion of cutaneous fat when lipids are fed over a long period. In this connection it is particularly interesting to note the clinical observations reported by Rattner[1127] and others that encephalitic processes are capable of causing extreme degrees of seborrhea and high grade, typical comedo formation. Stokes and Sternberg[1082] call attention to the fact that the activity of the sebaceous glands is to some extent dependent upon nervous control of the secretory function. Thus, emotional factors, notably depressive episodes, can give rise to high grade seborrhea. Furthermore, constipation, fermentative and putrefactive dyspepsia, and other abnormalities of digestion are likewise capable of increasing the seborrheic activity of the glands. The exact manner in which these disturbances exert their influence is not known. Some authorities believe that cutaneous hyperemia due to reflex mechanisms of varied etiology may constitute the underlying pathogenic basis.

The dietary management of seborrhea is very similar to that of acne vulgaris and, therefore, the reader is referred to Table 83 on page 492.

In addition to the diet, Barber[179] recommends a vigorous outdoor life with as much exercise as possible, light, porous underclothing, and a moderate amount of exposure of the skin of the whole body to the air and sunlight. All this serves to stimulate the oxidative function of the organism.

Of the various local measures, x-ray therapy and sulfur, preferably in a greaseless base (Pragmatar, Collo-Sul), are often very helpful.

1125. Sabouraud, R.: Entrétiens dermatologique à l'Ecole Lailler. Masson: Paris, 1922.
1126. Perutz, A., Lustig, B., and Klein, A. E.: Arch. f. Dermat. u. Syph. **170**: 511, 1934.
1127. Rattner, H.: Arch. Dermat. & Syph. **31**: 35, 1935.

C. HYPERIDROSIS

The term "hyperidrosis" denotes excessive production of sweat. This condition may be idiopathic or symptomatic. For idiopathic hyperidrosis, either generalized and localized, von Noorden[172] prescribes a diet very low in table salt. To begin with, the patient is put on a straight fruit diet for three or four days; then the so-called zigzag diet (p. 125) is instituted, in the course of which an entirely salt-free day is interposed between other days twice a week. Needless to say, the patient is at no time allowed to indulge in excessive quantities of table salt.

Von Noorden is of the opinion that the relative scarcity of sodium chloride in the blood, and thus also in the skin, serves to withdraw from the sweat glands one of the substances necessary for the production of sweat. He reports that cases in which hyperidrosis is localized in the hands and/or feet are, as a rule, particularly slow to respond to this type of dietary therapy.

Strong tea and alcohol should also be avoided, because they tend to promote sweating.

CHAPTER XIII

Diseases of the Cutaneous Blood and Lymph Vessels

In this category we group a number of heterogeneous dermatoses, some of which are of vascular origin (rosacea, lupus erythematosus, erythema multiforme, scleroderma, chilblain), others due to lymphatic disease (elephantiasis), and still others of hemorrhagic character (purpura).

A. ROSACEA

Rosacea is a chronic disorder of the skin of the nose and the flush area of the face, characterized by congestion (Fig. 277) and telangiectases and frequently accompanied by seborrhea and acneform inflammatory lesions (Fig. 228), (Sutton and Sutton[337]). This cutaneous disease is now generally regarded as an angioneurosis of the facial skin, occurring principally in seborrheic individuals (Becker and Obermayer[269]).

As yet nothing definite is known about its pathogenesis. According to Stokes and Beerman,[1128, 1129] nervous factors, gastrointestinal disturbances, focal infection, and overindulgence in caffein and hot beverages play major etiologic roles, while menstrual disturbances, condiments in excess, intolerance of the intestine for carbohydrates, vasomotor instability, alcoholism, and food allergy may also give rise to rosacea.

The neurogenous factor due to chronic worry, constant overwork, habitual late hours, insomnia, family troubles, introspective personality, marked repressions, excessive social responsibilities, sudden shock or emotion, which Stokes and Beerman found to be present in 76 per cent of their cases, is of particular significance here not only because of its harmful effect on vasomotor reactivity, but also because of its influence on the intestinal tract. Thus, Stokes and Pillsbury[734] found that their rosacea patients, when emotionally depressed, very often had gastric hypo-acidity.

Many authors have discussed the probable relationship between gastrointestinal disturbances and rosacea. Ryle and Barber,[1130] Brown,[757] Eastwood,[1131] Grintschar and Rachmanoff,[1132] Stokes and Beerman,[1128] and Urbach have reported instances of hypochlorhydria and achlorhydria in

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1128. Stokes, J. H. and Beerman, H.: Arch. Dermat. & Syph. **26:** 478, 1932.
1129. Beerman, H. and Stokes, J. H.: Arch. Dermat. & Syph. **29:** 874, 1934.
1130. Ryle, J. A. and Barber, H. W.: Lancet **2:** 1195, 1920.
1131. Eastwood, S. R.: Brit. J. Dermat. **40:** 91 and 148, 1928.
1132. Grintschar, F. N. and Rachmanoff, V. A.: Urol. & Cutan. Rev. **32:** 85, 1928.

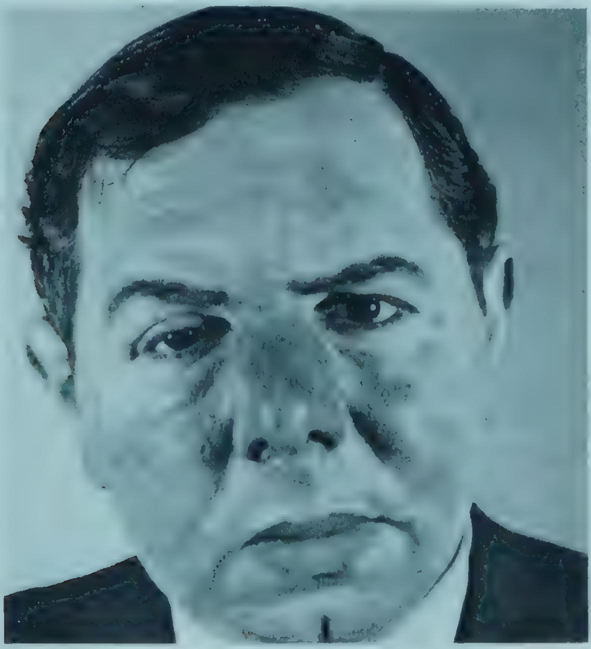

FIG. 227. ROSACEA

Note marked congestion.

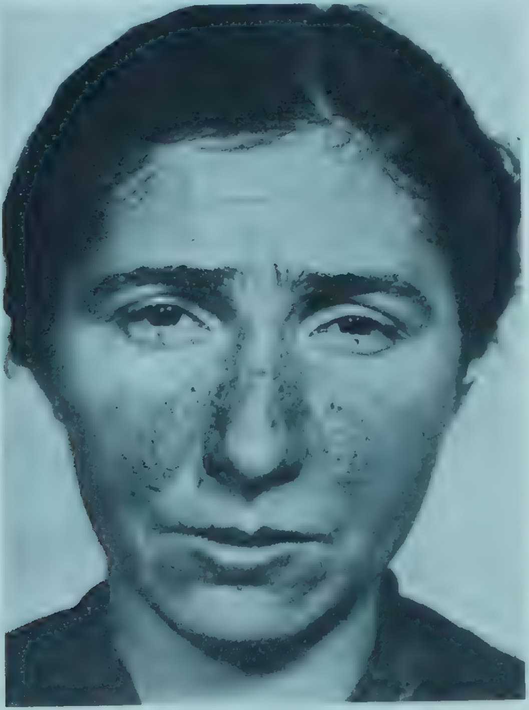

FIG. 228. ROSACEA

Showing acneform inflammatory lesions.

patients with rosacea. Occasional cases of hyperchlorhydria have also been observed (Sabouraud,[1133] Brown et al.,[1134] Urbach). Indeed, correction of the abnormal gastric secretion by suitable therapy will often be followed by improvement in the cutaneous condition.

[1133] SABOURAUD, R.: Presse méd. 25: 91, 1917.

[1134] BROWN, W. H., SMITH, M. S., and MCLACHLAN, A. D.: Brit. J. Dermat. 47: 181, 1935.

Usher[741] found gastritis of varying degrees of severity in eighteen of nineteen rosacea patients. In the great majority of these cases pronounced changes in the gastric mucosa were associated with some abnormality in hydrochloric acid secretion. Achlorhydria was always found in association with long-standing gastritis. Repeated gastroscopic visualization in two treated patients revealed coincidental improvement of the gastritis and the rosacea.

Other authorities are inclined to hold some dietary practices or certain foods responsible for the causation of rosacea. There are some (Bommer,[195] Schmid[1135]) who specifically incriminate diets too rich in meat or milk, basing their views on Gaensslen's[262] experimental findings that a diet high in protein leads to marked dilatation and abnormal permeability of the peripheral blood vessels, symptoms which retrogress completely on a fruit and vegetable diet. Eastwood[1131] is of the opinion that an excessively high carbohydrate diet is very common among patients with rosacea. Although Stokes and Beerman's patients were placed on a diet relatively low in carbohydrate, some 20 per cent of them exhibited intestinal and other symptoms strongly suggestive of Kendall's[1136] syndrome of intestinal intolerance for carbohydrates. This picture, which, according to Stokes, often corresponds to gastrointestinal symptoms so commonly seen in patients with rosacea, is associated with overgrowth of gas-forming organisms in the upper part of the intestinal tract and indicates abnormal utilization of carbohydrate by the intestinal flora, rather than a disordered carbohydrate metabolism. For this reason Stokes and Beerman advocate a sharp and lasting restriction of carbohydrates, large doses of hydrochloric acid, and the encouragement of an acidophilic intestinal flora. In this connection it is interesting to note LeWinn's case[1136a] of hyperinsulinism which also presented marked rosacea of fifteen years' duration. Incidental to treatment of the endocrine disturbance with a high fat, low carbohydrate diet plus insulin in small doses, the rosacea improved almost to the point of disappearance.

A third group of investigators, composed chiefly of French clinicians (Brocq,[2] Sabouraud,[1133] Darier,[1137] Hermans and Belinfante[1085]), has attributed this disease to chronic constipation, intestinal fermentation, and putrefaction. Ramel[1138] also advocates the avoidance of foods and beverages causing fermentation. Darier[1137] is inclined to incriminate the digestive disturbances due to biliary disease.

1135. Schmid, E.: Dermatologica **83:** 95, 1941.
1136. Kendall, A. I.: J. A. M. A. **86:** 737, 1926.
1136a. LeWinn, E. B.: Am. J. Med. Sc. **196:** 217, 1938.
1137. Darier, J.: Précis de Dermatologie. Paris: Masson, 1923.
1138. Ramel, E.: Schweiz. med. Wchnschr. **69:** 1283, 1939.

As Ayres, Jr.,[1139] has pointed out, there is an intimate reflex connection between the stomach and the vascular supply of the face. While the mere taking of food into the stomach frequently tends to cause flushing of the central portion of the face, certain foods and beverages are particularly likely to set this reflex mechanism in motion. Alcohol, even in minute quantities, is the greatest offender; coffee and strong tea stand in second place; iced as well as excessively hot drinks often cause facial congestion; and condiments unquestionably play a significant role. Moreover, Lortat-Jacob and Legrain[1140] emphasize the importance of eating food slowly and of sipping drinks.

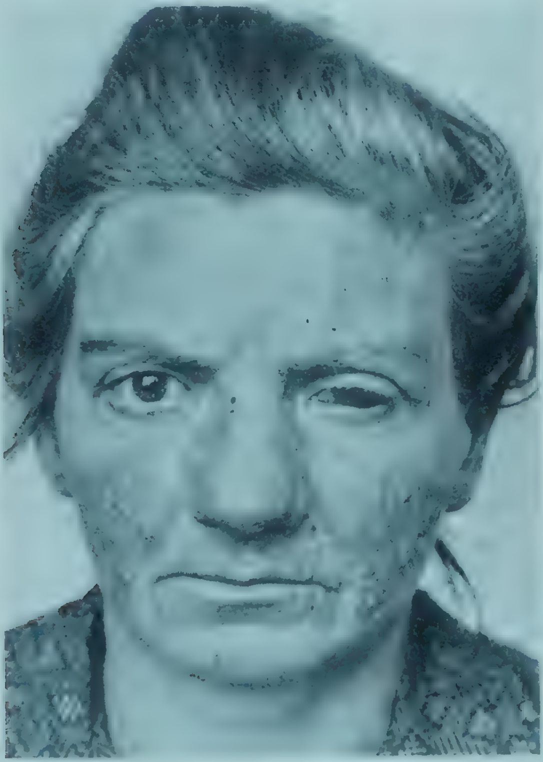

FIG. 229. SEVERE ROSACEA WITH ROSACEA KERATITIS

According to Stokes and Beerman,[1128] Bommer,[195] and Ramel,[1138] occasional cases of rosacea are demonstrably due to food allergy.

While the ocular manifestations which are so frequently encountered in rosacea patients (rosacea keratitis, Fig. 229) respond well to medication with riboflavin, the cutaneous lesions themselves are in no way influenced by this vitamin treatment (Conners et al.,[128] Chana and Verdaguer[1141]). However, Mashkilleison[405] reported that a combination of riboflavin (50

1139. AYRES, S. JR.: in BRIDGES, M. A.: Dietetics for the Clinician. Philadelphia: Lea and Febiger, 1941.
1140. LORTAT-JACOB, L. and LEGRAIN, P.: Progrès méd. **38:** 143, 1923.
1141. CHANA, P. and VERDAGUER, J.: Rev. argent. dermatosif. **26:** 51, 1942.

mg. three times daily) and niacin (100 mg. three times a day), given orally, had a beneficial effect on the facial rosacea.

From the foregoing it is evident that the therapy of rosacea should include: (1) adjustment of the neurogenous background; (2) correction of gastrointestinal disturbances by means of administration of hydrochloric acid in hypochlorhydria, or of antacids in hyperchlorhydria, plus the respective, indicated diets (see p. 302); correction of constipation, fermentation and putrefaction by dietary measures; (3) a trial with a fruit-vegetable-carbohydrate diet, containing small amounts of protein and fats; (4) the use of a low carbohydrate diet, if the fruit-vegetable-carbohydrate diet proves ineffective; (5) strict prohibition of alcohol, coffee, strong tea, soft drinks, smoked and canned meat and fish, grease, lard, tallow, margarine, cheese, salt, condiments, and highly seasoned and fried foods; (6) avoidance of hot and cold foods and beverages; (7) training the patient to eat and drink slowly.

In addition to these general rules, it should be remembered that menstrual disturbances, focal infections, or allergies must be properly dealt with. Lastly, local therapy, consisting chiefly of sulfur and resorcinol lotions, should be instituted to control the seborrhea of the scalp and face.

B. LUPUS ERYTHEMATOSUS

Lupus erythematosus is a systemic disease the effects of which are most conspicuously reflected in the smaller blood vessels of the skin and viscera. The basic pathologic change seems to consist of necrotizing damage to the small vessels with subsequent thrombosis and hemorrhage (Baehr and co-workers[1142]). The question as to whether this condition is fundamentally due to infection or to allergy (possibly through some bacterial-allergic mechanism) is still highly controversial (Stokes, Beerman, and Ingraham[1143]).

Many different remedial measures have been recommended for the treatment of lupus erythematosus. Here we are concerned only with the influence of nutritional and vitamin therapy. Kerl[1144] has reported an exceptionally refractory case of lupus erythematosus in a man who was discharged from the hospital in a very satisfactory condition after a period of strict adherence to Sauerbruch and Herrmannsdorfer's salt-poor diet (see p. 70). The patient should be informed that a few days after institution of this nutritional therapy there is not infrequently a pronounced exacerbation, which, however, promptly subsides. Jaffe,[1145] Delbanco,[1146]

[1142] Baehr, G., Klemperer, P. and Shifrin, A.: Tr. A. Am. Phys. **50:** 139, 1935.

[1143] Stokes, J. H., Beerman, H. and Ingraham, N. R. Jr.: Am. J. M. Sc. **207:** 540, 1944.

[1144] Kerl, W.: Zentralbl. f. Haut- u. Geschlechtskr. **37:** 791, 1931.

[1145] Jaffe, K.: Zentralbl. f. Haut- u. Geschlechtskr. **34:** 129, 1930.

[1146] Delbanco: Zentralbl. f. Haut- u. Geschlechtskr. **32:** 559, 1930.

Loehe,[990] Ayres, Jr.,[1139] Blumenthal et al.,[1147] and others have also found appreciable improvement on a low salt diet. In addition to a number of highly gratifying results which may well have been due to nonspecific alteration of the organism as a whole, we have observed many patients in whom the gains registered on a salt-poor diet were lost soon after discontinuance of such dietary therapy and not a few instances in which this diet proved entirely ineffective, even as an adjuvant therapeutic measure. However, since this regimen cannot harm the patient in any way, it is always worth a trial in severe, therapy-resistant cases.

Gross,[840] Andrews,[1065] and Cannon[1148] obtained good results with intramuscular injections of crude liver (3 cc. twice weekly). This treatment may be profitably supplemented with niacin (100 mg. three times a day) administered over a long period of time (Stokes[440]). In cases exhibiting definite signs of hypersensitiveness to light, Andrews[1065] found riboflavin to be particularly beneficial. In especially severe cases it may be necessary to give all the individual members of the vitamin B complex plus liver extract. Gross and Kesten[124] have contributed a description of the following typical and instructive case:

> The patient, a chronic alcoholic, presented an extensive eruption of subacute lupus erythematosus. Liver damage was evidenced by a positive cephalin flocculation test. There was a high serum cholesterol level. In addition, he had a moderate degree of macrocytic hyperchromic anemia, typical polyneuritis due to thiamine deficiency, and a high urinary coproporphyrin level. Treatment consisted of 20 injections of liver extract, 5 injections of iron adenylate, ferrous sulfate, brewers' yeast, thiamine, synthetic B complex of high potency, and intravenous injections of pyridoxine. All clinical signs disappeared, the cephalin flocculation test became negative, and the serum cholesterol levels returned to normal.

In the presence of hypoproteinemia, large amounts of protein should be given in addition to vitamin therapy. Moreover, a high caloric, high vitamin diet is recommended.

Lastly, mention must be made of a very strange diet which was instituted by a food faddist. In the judgment of two such outstanding clinicians as Anderson and Ayres, Jr.,[1149] this diet was largely responsible for the good results obtained in six cases either of lupus erythematosus or of actinic dermatitis. Just what this diet does, Anderson and Ayres did not venture to state. It may be that it exerts its favorable influence by bringing about changes in the mineral metabolism, by supplying needed vitamins, or by changing the intestinal flora.

> The prescribed regimen was as follows: 7 a.m., 1 teaspoonful of "vegetable salt" in a glass of hot water. At 8 a.m., 1 glass of orange juice. Some kind of fruit every

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1147. Blumenthal, F., Boehmer, L., and Hoefer, C.: Delib. 8th Internat. Dermat. Congress, p. 461, 1903.
1148. Cannon, A. B.: Arch. Dermat. & Syph. **51:** 26, 1945.
1149. Anderson, N. P. and Ayres, S. Jr.: J. A. M. A. **103:** 1279, 1934.

hour until noon. At 12 noon, a salad of raw vegetables plus 2 cooked vegetables. A piece of fruit or a glass of fruit juice every hour in the afternoon. At 6 p.m., a salad of raw vegetables plus 2 cooked vegetables; prunes, baked apple, or other fruit. The patient is allowed to drink at any time a vegetable broth prepared in the following manner: 3 cups of carrots, 3 cups of celery, one cup of spinach, and ½ cup of parsley, all ground fresh and then put into 2 quarts of luke-warm water and allowed to simmer over a low flame for not more than 25 minutes. The broth is allowed to stand for one hour and is then strained through cheesecloth. The residue is thrown away. Tomato juice or juices from ground raw vegetables are added to the broth. Such a regimen is, of course, similar to the salt-poor diet of Sauerbruch-Herrmannsdorfer referred to above.

C. ERYTHEMA MULTIFORME

Erythema multiforme is a clinical rather than an etiologic entity; in other words, the manifestations of this disease may be produced by a variety of causes. However, it is now generally agreed that the condition involves vascular hypersensitivity (Becker and Obermayer[269]).

One of the causes seems to be allergy. As early as 1900, Osler[1150] described cases presenting symptoms of urticaria, angioneurotic edema, colic, and asthma simultaneously. There have been a number of reports that erythema multiforme appeared after certain foods were eaten. Galloway[1151] described a case of erythema multiforme following ingestion of black currants and nuts; Engman[1152] and Klauder,[1153] of pork; Fordyce,[1154] of lobster; and Klauder[1155] of shrimps.

Whether the manifestations in a given case are actually due to an allergic reaction or constitute an exanthem of toxic nature can be determined only by readministering the same food after the cutaneous manifestations have disappeared; if the symptoms reappear, the allergic origin is demonstrated.

Bulkley,[5] who was himself a victim of this disease, observed in his own case as well as in others suffering from bullous erythema multiforme that strict adherence to a diet of rice and water brought marked improvement. He also prescribed a laxative.

Keining and Oldach[1156] divide cases of erythema multiforme into two groups on the basis of their response to niacin: (1) those presenting the typical prodromal symptoms of follicular tonsillitis and rheumatoid symptoms, which do not seem to be closely dependent upon seasonal influences and which do not respond favorably to niacinamide; and (2) those of the so-called annual type, which readily respond to niacinamide (100 mg.

1150. Osler, W.: Brit. J. Dermat. **12:** 227, 1900.
1151. Galloway, J.: Brit. J. Dermat. **15:** 235, 1903.
1152. Engman, M. F.: J. Cutan. Dis. **30:** 166, 1912.
1153. Klauder, J. V.: Arch. Dermat. & Syph. **19:** 198, 1929.
1154. Fordyce: Arch. Dermat. & Syph. **2:** 571, 1920.
1156. Keining, E. and Oldach, F. A.: Dermat. Wchnschr. **112:** 285, 1941.

intramuscularly daily), have a definitely seasonal incidence, and are not accompanied by tonsillar or rheumatoid manifestations. The exact nature of the role played by niacin in the latter group of cases is a matter of conjecture.

D. SCLERODERMA

The term "scleroderma" refers to a group of diseases, all of which are characterized by the following sequence: primary vascular changes followed by connective tissue hyperplasia, which, in turn, leads to circumscribed or diffuse boardlike hardening of the skin.

While the condition does not as a rule respond satisfactorily to treatment, there are a few isolated reports which suggest that nutritional therapy may exert a favorable influence. On page 346 we discuss at some length Sellei's theory that the form of scleroderma in which the vasospastic phenomena appear early and are outstanding—the picture for which Sellei[849] and O'Leary and Waisman[1157] propose the term "acrosclerosis"—is a dysfermentosis. On this assumption, the Hungarian author introduced a ferment treatment consisting chiefly of raw pancreas, hydrochloric acid, pepsin, and certain metallic catalysts. Becker and Obermayer[269] reported satisfactory results with Sellei's method in two cases of generalized, superficial scleroderma. The present writer is also inclined to be encouraged by this approach. His patients have had the impression that the hardness of the skin was subsiding to some extent.

Cornbleet and Struck[531] reported that large doses of vitamin D given over a long period of time serve to promote the excretion of calcium and have a beneficial influence. The present writer can recommend intravenous injections of 100 mg. of niacin, but not niacinamide, because the flushing effect of the former is desirable, together with regular massages. Ormsby and Montgomery[915] advocate a well balanced and nutritious diet supplemented by vitamins.

E. CHILBLAIN

Pernio, or chilblain, is a disorder generally occurring on the hands, feet, and ears of persons with poor peripheral circulation. This condition is also commonly encountered in inadequately nourished individuals who are exposed to damp or cold weather.

Because a constitutional defect is the underlying cause of this disease, treatment must be general as well as local. Therefore, in addition to topical remedies, there should be prescribed measures designed to improve the patient's general condition, such as active exercise and a diet high in calories and vitamins. Since niacin is known to improve the peripheral

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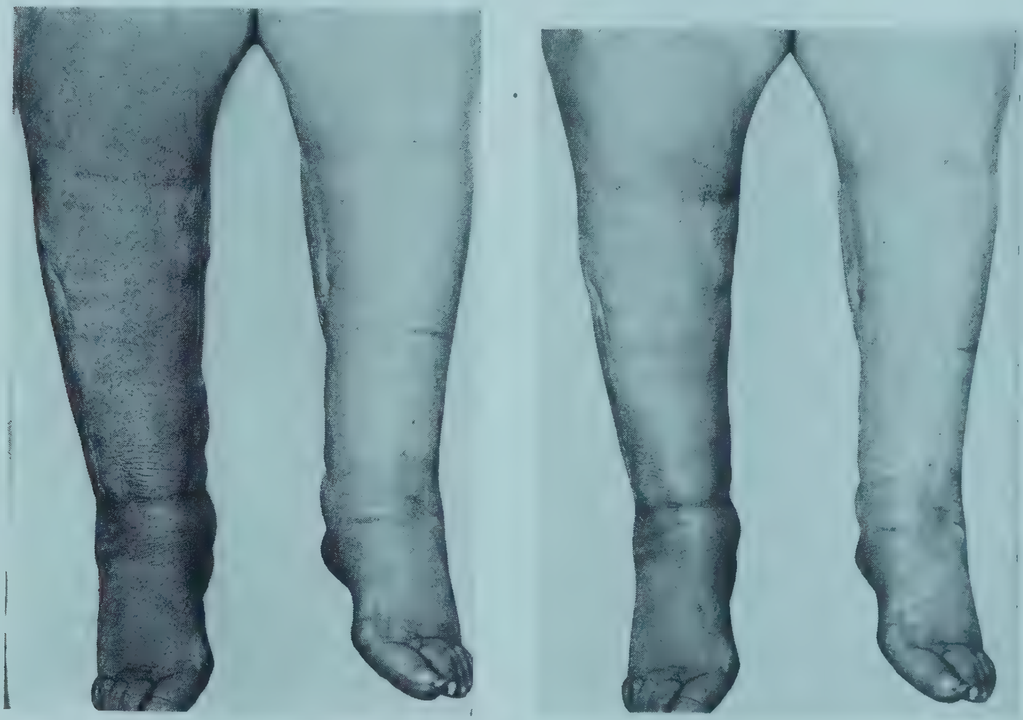
1157. O'Leary, P. A. and Waisman, M.: Proc. Staff. Meet. Mayo Clin. 15: 702, 1940.

circulation, Birkhauser[1158] gave this vitamin intravenously and observed improvement after several injections. In many instances similar good results were seen by Jausion and co-workers.[1159] It is believed that niacin, but not niacinamide, improves peripheral circulation.

Krasper[1160] saw chilblains of many years' standing retrogress on a diet low in table salt. When the diet was adhered to faithfully, the chilblains did not reappear the following winter.



ELEPHANTIASIS

FIG. 230. Before treatment.

FIG. 231. After twelve weeks of strict Sauerbruch-Herrmannsdorfer diet.

F. ELEPHANTIASIS

Elephantiasis is a chronic disease of the skin and the subcutaneous tissue, characterized by lymphatic stasis and secondary hyperplasia of the involved structures. In cases resulting from venous thrombosis or local tissue injury, a trial with a salt-poor diet accompanied by sharp restriction of the liquid intake (as outlined in Schroth's diet, see p. 126) is indicated. In occasional cases the present writer has noted a definite response to this form of treatment (Figs. 230, 231).

1158. BIRKHÄUSER, H.: Schweiz. med. Wchnschr. **72:** 1280, 1942.
1159. JAUSION, SOMIA, and MEUNIER: Presse méd. **49:** 484, 1941.
1160. KRASPER: cited by BOMMER: München. med. Wchnschr. **82:** 1683, 1935.

CHAPTER XIV

Purpura

DEPENDING on the blood picture, purpuras are conventionally divided into two main groups: the nonthrombocytopenic and the thrombocytopenic. Here, needless to say, we shall discuss only those purpuras which are of nutritive-allergic or nutritive-toxic origin. In the nonthrombocytopenic group, a nutritive-allergic mechanism can be demonstrated in occasional cases of purpura simplex. Thus, Sachs[599] and Rowe[25] have described petechial eruptions following ingestion of anchovies. Landsberger[1161] saw petechial hemorrhages in the skin, as well as in the mucosa of the mouth and throat, make their appearance eight days after a nursling had first received cow's milk. These symptoms vanished when mother's milk was substituted, but reappeared when the infant was again given cow's milk. Figure 232 shows purpura due to hypersensitiveness to mutton.

Nutritive-allergic purpura can readily be differentiated from the nutritive-toxic form (due to spoiled food) by the fact that the manifestations in the former appear after every ingestion of the food in question, while the symptoms of toxic purpura are elicited only by one accidental exposure. Figure 233 demonstrates a severe purpura after ingestion of large amounts of saffron in order to induce abortion.

More often than not, allergy to some food will be found to be the cause of Henoch's purpura. This term denotes a syndrome in which purpuric attacks (Fig. 234) are associated with visceral and joint manifestations. In experiments on a group of cases, Alexander and Eyermann[1162] demonstrated that elimination of certain foods from the patients' diet prevented the purpura and accompanying intestinal attacks, while these symptoms promptly reappeared following ingestion of the foods in question. Similar observations have been reported by Kahn,[1163] Barthelme,[1164] Kern,[1165] Hampton,[1166] and others.

Vitamin deficiency is an important cause of purpura of nonthrombocytopenic origin. It is, of course, well known that a deficiency in vitamin C, P, or K may lead to rather severe cutaneous and internal bleeding. Table 85 presents the differential features of the purpura due to these three vitamins.

[1161] LANDSBERGER, M.: Ztschr. f. Kinderh. **39:** 569, 1925.

[1162] ALEXANDER, H. L. and EYERMANN, C. H.: J. A. M. A. **92:** 2092, 1929.

[1163] KAHN, I. S.: J. Lab. & Clin. Med. **14:** 835, 1929.

[1164] BARTHELME, F. L.: J. Allergy **1:** 170, 1930.

[1165] KERN, R. A.: in discussion to Hampton[1166].

[1166] HAMPTON, S. F.: J. Allergy **12:** 579, 1941.

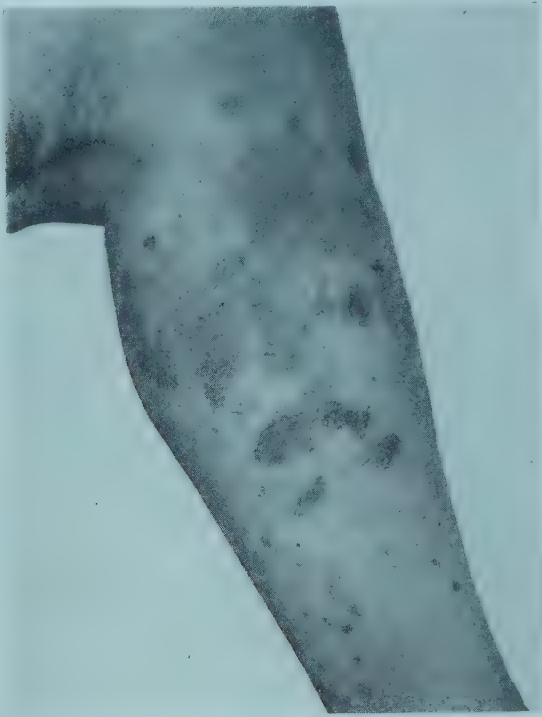


Fig. 232. Purpura Due to Mutton Hypersensitiveness

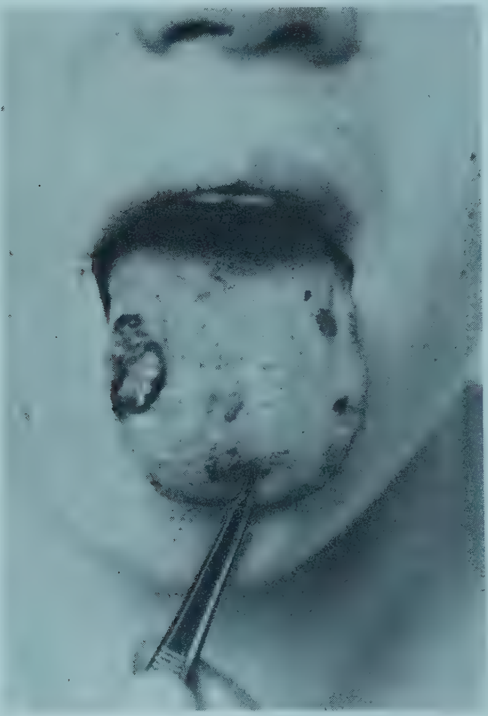


Fig. 233. Purpura Following Ingestion of Large Quantities of Saffron

Thrombocytopenic purpura is only rarely due to food allergy. However, Squier and Madison[1167] reported three cases in which milk, potato,

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1167. Squier, T. L. and Madison, F. W.: J. Allergy 8: 143, 1937.

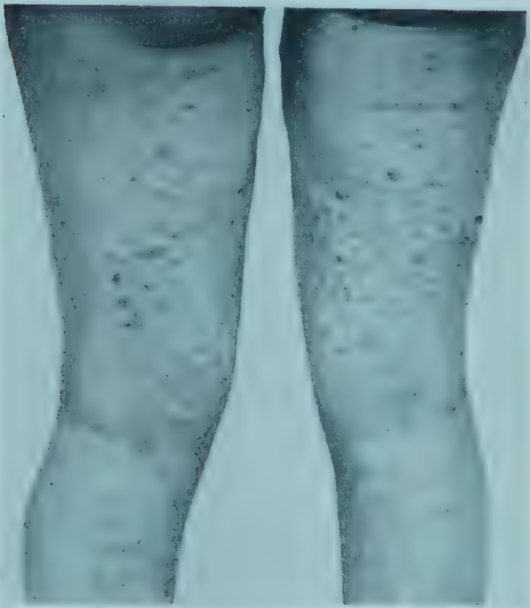


FIG. 234. HENOCH'S PURPURA
The patient complained of visceral and joint symptoms coincident with the skin lesions.

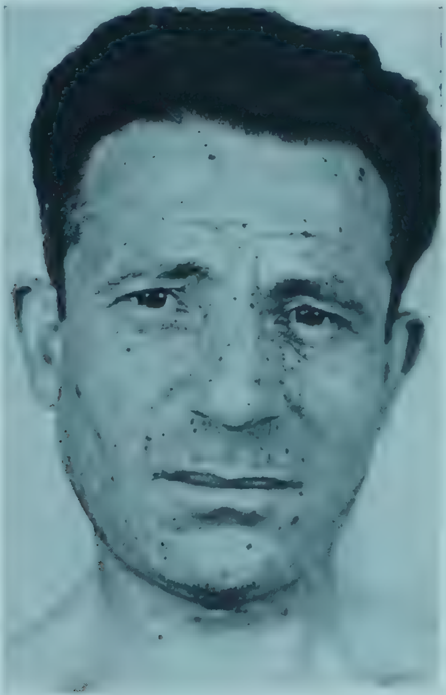


FIG. 235. THROMBOCYTOPENIC PURPURA DUE TO EGG ALLERGY

wheat, cocoa, and egg were identified as the allergens; and Dutton[1168] has described one case demonstrably due to citrus fruits. Figure 235

[1168] DUTTON, L. O.: J. A. M. A. 11: 1920, 1938.

TABLE 85.—*Differential Features of Purpura of Vitamin-Deficiency Origin (Jeghers*[322]*)*

Differential Features	Vitamin K Deficiency		Vitamin C Deficiency	Vitamin P Deficiency
	Latent Hemorrhagic Hypoprothrombinemia (Bleeding Only after Trauma)	Spontaneous Hemorrhagic Hypoprothrombinemia (Spontaneous Bleeding)		
Chief reason for development of the vitamin deficiency	Liver disease, obstructive jaundice, sprue, diarrhea, high fever, infancy (newborn), and so forth	Liver disease, obstructive jaundice, sprue, diarrhea, high fever, infancy (newborn), and so forth	Dietary deficiency	Dietary deficiency
Factors conditioning the appearance of the purpura	At sites of obvious trauma, such as recent wounds (operative, traumatic, and so forth), intestinal ulcers (ulcerative colitis), needle puncture areas of skin, vigorous brushing of teeth, and so forth	Appears spontaneously, with little or no trauma in skin, mucous membranes, brain, uterus, and so forth	Orthostatic in legs from pressure or trauma to skin; may also appear spontaneously without obvious trauma	Orthostatic in legs; may appear spontaneously or follow pressure on the skin
Dermal manifestations of the purpura	As above: needle puncture ecchymosis or hematoma is the most characteristic skin lesion in the average patient; no petechiae	Ecchymoses and suffusions of blood in skin, especially over pressure areas; skin purpura not always a prominent feature; may be minimal although serious internal bleeding is present; no petechiae	Ecchymoses of skin and soft tissues; perifollicular hemorrhages	Petechiae the chief lesion; may be spontaneous or appear over pressure areas; may be perifollicular in location
Spontaneous mucous-membrane bleeding	Absent	Present	Present	Absent
Gums	Normal; no bleeding except from trauma	Gums relatively normal in appearance; may appear hemorrhagic and bleed spontaneously but are not heaped up, spongy, or purplish	In association with gingival disease are spongy, heaped up, and purplish; may be normal in the edentulous or well kept mouth	Normal
Perifollicular localization of hemorrhagic diathesis	Absent	Absent	Present	Present

Blood prothrombin level	Below 35 per cent of normal	Below 20 to 15 per cent of normal	Normal	Normal
Clotting time	Generally normal	Commonly prolonged	Normal	Normal
Clot retraction	Normal	Normal	Normal	Normal
Plasma and white cell platelet vitamin C content	Normal	Normal	Very low to absent	Normal
Bleeding time (Duke)	Normal at the time of test; bleeding may occur from the puncture wound after an interval of time	Usually normal, occasionally prolonged; bleeding may occur from the puncture wound after an interval of time	Normal	Slightly prolonged
Platelet count	Normal	Normal	Normal but may be somewhat diminished at times (values as low as 100,000 per cubic millimeter have been noted clinically	Normal
Tourniquet test (Rumpel-Leed)—petechiae appearing after application of a tourniquet to the arm	Normal	Normal	Normal	Strongly positive; many petechiae appear below level of the tourniquet
Comment	A slight diminution of the prothrombin content of the blood may result from a pure nutritional deficiency of vitamin K, but probably never or only rarely will it be of a degree sufficient to cause bleeding; it may, however, be additive to the causes listed above.		Scurvy, as seen clinically, may represent varying combinations of the features of both these deficiencies	

demonstrates thrombocytopenic purpura due to egg and Figure 236 due to anchovies.

The only effective method of treating the nutritive-allergic forms of purpura is to discover and eliminate the allergen. If the causal food is an important one, an attempt to deallergize the patient with the type-specific Propeptans is indicated (p. 267). In cases with demonstrable vitamin deficiency treatment naturally consists of administration of foods containing an abundance of the vitamin in question and, at least in the earlier stages of treatment, of appropriate doses of the required vitamin or vitamins.

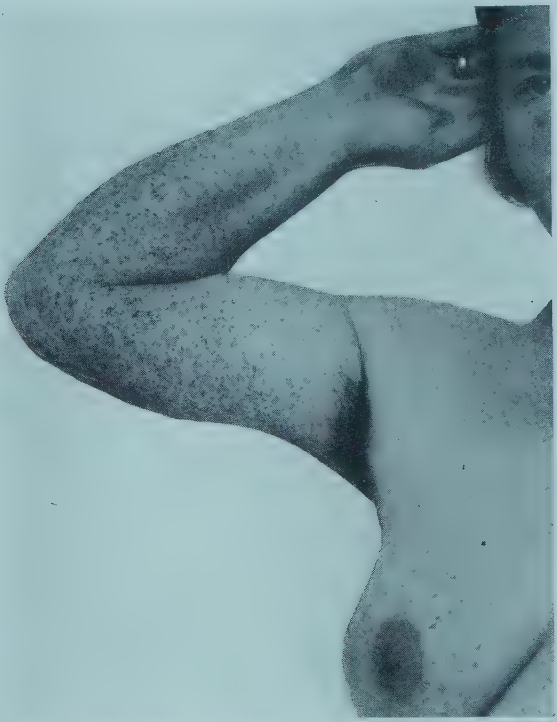


FIG. 236. THROMBOCYTOPENIC PURPURA DUE TO FISH HYPERSENSITIVENESS

CHAPTER XV

Lichen Planus

In cases of lichen planus which fail to respond to the conventional measures, nutritional therapy may well be worth trying. The literature contains a number of reports that the low salt diet of Sauerbruch and Herrmannsdorfer (p. 70) or Bulkley's rice diet (p. 104) has proved to be distinctly beneficial (Volk,[1169] Keining and Hopf,[1170] Kren,[1171] Serefis,[1172] Bulkley,[5] Urbach). In some instances these dietary measures brought on severe exacerbation of the lesions, followed, however, by spectacular improvement (Volk[1169]). Keining and Hopf[1170] as well as Eller and Rein[188] found the equilibrated salt diet (p. 67) to be as effective as the low salt regimen.

Burgess[1173] and Gross[840] approach the problem differently. These authors give vitamin B complex in acute and chronic cases alike, and have reported satisfactory results. Tzank et al.[1174] and Gross[840] have observed some cases in which extensive lesions yielded promptly to nicotinic acid, either alone or in combination with a potent B complex preparation.

[1169] Volk, R.: Dermat. Wchnschr. **91:** 1869, 1930.

[1170] Keining, E. and Hopf, G.: München. med. Wchnschr. **78:** 1036, 1931.

[1171] Kren, O.: Zentralbl. f. Haut- u. Geschlechtskr. **36:** 163, 1931.

[1172] Serefis, S.: Dermat. Ztschr. **64:** 387, 1932.

[1173] Burgess, J. F.: Canad. M. A. J. **44:** 120, 1941.

[1174] Tzank, A., Sidi, A., and Tardieu, G.: Bull. Soc. franc. de dermat. et syph. **46:** 862, 1939.

CHAPTER XVI

Light Dermatoses

Actinic dermatoses in man can take the form of acute, subacute, or chronic dermatitis, urticaria, lupus erythematosus-like eruptions, hydroa vacciniforme, summer prurigo, and certain pigmentary disturbances. The pathogenesis of the light dermatoses is as yet rather obscure. However, it has been observed time and again that correction of hepatopathy, gastrointestinal disease, endocrine dysfunction, infection, or intoxication is followed either by complete cure or at least by temporary disappearance of the hypersensitiveness to light. It is generally assumed that in cases of this kind the improvement may be attributed to arrest or interruption of the formation of photosensitizing or photodynamic substances. Here we are concerned principally with those cases in which the diet is a factor, either because certain foods contain a photodynamic substance or because institution of appropriate dietary measures (e.g., a liver-sparing diet) serves to halt the production of photosensitizing substances due to some pathologic metabolic process in an internal organ (e.g., the liver).

Light dermatoses caused by ingestion of photosensitizing substances contained in food are encountered almost exclusively in animals (cattle, pigs, sheep) and are generally found to be due to certain plants such as buckwheat (*Fagopyrum*), St. Johns-wort (*Hypericum*), wilted "dubbeltje" plant (*Tribulus*), clover (*Trifolium*), agave (*Agave lechuguilla*), and paintroot (*Lachnanthes*). The clinical picture was discussed in some detail on page 288. Rats, fed on a diet containing 90 per cent of ground whole buckwheat seeds, showed a high degree of sensitivity when exposed to sunlight or to carbon arc lamp irradiation. No symptoms were observed when the husks were removed from the seeds. The dried leaves had no photosensitizing effect. The young flower was found to be the most active in this respect. The sensitizing rays were located in the yellow-orange portion of the visible spectrum. The minimum single sensitizing dose of dried flowers was 0.25 mg. per 100 Gm. of animal. The sensitizing pigment was easily destroyed by heat or alkali and was soluble in alcohol (Chick and Ellinger). In man these diseases are virtually unknown, probably owing to the fact that the active agent is altered in the cooking process and thus rendered harmless. However, it may be pertinent to mention Bommer's[195] observation that an increase in the incidence of light hypersensitiveness occurred primarily in the spring, when his patients were put on a diet of raw foods. Bommer is of the opinion that this may be explained by the fact that such a diet leads to an increased consumption of chlorophyll, which, in turn, may exert a photodynamic influence. Moreover, xanthodermia lipochromica may well be due, at least in part, to the influence of light. Thus, Klose[328] observed in infants a yellow discoloration following ingestion of carrots and appearing only in those areas that were exposed to fairly strong sunlight, that is to say, principally the face. Moreover, this coloration was seen almost exclusively in the summer and notably in infants whose cribs were placed near a window. Similarly, Hess and Myers[316] and Dollinger[327] assume that light plays a role in those cases in which, following ingestion of large amounts of spinach, a greenish coloration of the skin makes its appearance only in those areas that have been exposed to sunlight, such as the forehead, nose, cheeks, and hands.

It is possible that a similar mechanism occurs in Riehl's "war melanosis." This term refers to a dermatosis first observed by Riehl, Sr.,[1175] during World War I, and attributed by him to a toxic alimentary factor arising from the ingestion of a substitute material (beans) used in Austria for making bread. Blaschko[1176] concurs but feels that other foods must be held equally responsible, especially the various substitute materials used in the manufacture of margarine. Kerl,[1177] on the other hand, assumes that this dermatosis may be attributed to the presence in the ingested foods of photodynamic substances which sensitize the exposed skin areas to sunlight. It is noteworthy that this disease virtually disappeared when the food situation returned to normal in Austria and Germany, which justifies Riehl's use of the term "war melanosis."

In this connection we should like to cite a clinical observation of Reiss,[716] who noted that in well-to-do Chinese x-ray therapy frequently was followed by very marked cutaneous pigmentation. Chinese of this class partake of a diet rich in soy beans, which, according to Reiss' investigations, seem to contain a fluorescent pigment which may act as a sensitizer responsible for the pigmentary changes.

Far more important, however, are the relatively numerous cases in which the actinic dermatosis is apparently due to an underlying hepatic disorder or gastrointestinal disease. Thus, Barber[1178] has reported the illustrative case of a man who, following overindulgence in alcohol, exposed himself to sunlight and acquired light dermatitis. The liver was greatly enlarged and the urine was found to contain quantities of urobilin. After the patient had adhered to a strict diet for some time and completely abstained from alcoholic beverages, the liver showed great improvement

1175. Riehl, G.: Dermat. Wchnschr. **66:** 338, 1918.
1176. Blaschko, A.: Dermat. Wchnschr. **66:** 338, 1918
1177. Kerl, W.: Arch. f. Dermat. u. Syph. **130:** 436, 1921.
1178. Barber, H. W.: Practitioner **128:** 209, 1932.

and the photosensitivity soon vanished. Barber, Howitt, and Knott[1179] have reported a number of cases in which treatment of gastrointestinal disease was followed by marked retrogression of the skin manifestations caused by light hypersensitiveness, which these authors attributed to a bacterial toxin formed in the intestine. The present writer[788] has described a syndrome consisting of light dermatosis, hepatopathy, intestinal dysbacteria, and fecal porphyria. The remarkable thing about these cases, of which we have seen about a dozen, is the fact that the porphyrin was present almost exclusively in the feces and relatively rarely in the urine after the patients had been kept on a meat-free diet for three days. Porphyrin disappeared, however, following a strict animal protein–free diet which excluded such foods as meat, fish, poultry, eggs, milk and cheese for a period of four to five weeks. This diet is further characterized by its liver-sparing qualities; that is, it contains an abundance of sugar and other carbohydrates, but no animal or vegetable fats. In addition to these dietary measures, Bacillus acidophilus preparations or Mutaflor (viable normal B. coli cultures) should be given to correct the pathologic intestinal flora in which the normal colon bacillus has been replaced either by hemolytic B. coli or, what is more important, by streptococci and staphylococci. The B. acidophilus preparations should be taken together with lactose (1 tablespoonful at each dose) in order to encourage the establishment of B. acidophilus in the intestinal flora. Buttermilk may also be tried. According to Schreus,[818] treatment should also include administration of liver by mouth or injection of crude liver extract (3 cc. every second day). In cases with hepatic disease the present writer supports the liver by the use of regular insulin (10 units three times a day) a short while after ingestion of adequate amounts of carbohydrates. With this treatment we have been able to obtain a gratifying response as shown by marked retrogression of the cutaneous symptoms together with complete disappearance of fecal and urinary porphyrin, even in very severe actinic dermatoses of many years' duration. The beneficial effect of a strict vegetable and fruit diet, reported by Anderson and Ayres,[1149] may be attributed to similar basic principles.

In addition to the dietary measures mentioned above, niacinamide (in doses of 100 mg. three times a day) is often very helpful (Gilman,[439] Stokes[440]). O'Leary,[1180] Capps and Young,[1181] and Epstein[1182] have observed encouraging results obtained with histaminase (10 units three times a day given from March until September). The writer has seen two cases in which this preparation led to remarkable improvement, although in many others there was no response.

[1179] Barber, H. W., Howitt, F. D., and Knott, F. A.: Guy's Hosp. Rep. **76:** 314, 1926.

[1180] O'Leary, P. A.: in discussion to Laymon, C. W. and Cumming, H. A.: J. Invest. Dermat. **2:** 301, 1939.

[1181] Capps, R. B. and Young, R. H.: Proc. Am. Soc. Clin. Invest. **19:** 778, 1940.

[1182] Epstein, S.: J. Invest. Dermat. **5:** 187 and 225, 1942.

Russakoff and Blumberg[1183] have reported that, in conjunction with dietary and vitamin therapy, the use of choline chloride (3 Gm. two times daily by mouth) is of benefit in cirrhosis of the liver. LeWinn, who has employed this therapy in infectious hepatitis, believes it to be a valuable adjunct.

In some cases removal of an infected gallbladder (Urbach and Shay,[800] Fig. 237), correction of menstrual disturbances (Lancaster,[1184] Thurmon,[1185] Brunsting[1186]), removal of systemic and focal infections (Stokes and Callaway,[1187] Sonck[1188]), or improvement of the function of a syphilitic liver by antiluetic therapy (Urbach and Bloech[812]) may serve to eradicate the hypersensitiveness to light.

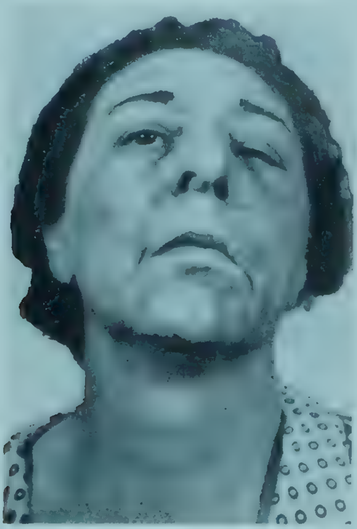


Fig. 237. Light Hypersensitiveness Cured by Cholecystectomy

We present in detail two cases which illustrate the beneficial influence of the dietary and other treatment described above on the clinical picture of light dermatosis, porphyrinopathy, hepatopathy, and the pathologic intestinal flora.

Case 1. A 50 year old man, whose father had also suffered from rather severe light hypersensitiveness, gave a history of attacks of biliary colic and migraine of many years' duration. Following tonsillectomy which was done because of an arthritis of the spine, there appeared on the exposed areas of the body a severe dermatitis which finally assumed an erythrodermatitic character. The light hypersensitiveness became so distressing that the patient was forced to stay in a dark room for nine months.

[1183] Russakoff, A. H. and Blumberg, H.: Ann. Int. Med. **21:** 848, 1944.

[1184] Lancaster, A. H.: South. M. J. **32:** 495, 1939.

[1185] Thurmon, F. M.: Section on Dermatology, A. M. A., June 12, 1942.

[1186] Brunsting, L. A.: in discussion to Thurmon[1185].

[1187] Stokes, J. H. and Callaway, J. L.: Arch. Dermat. & Syph. **36:** 976, 1937.

[1188] Sonck, C. E.: Acta dermat.-venereol. **22:** 499, 1941, suppl. 6.

On admission to the hospital the patient presented an extremely severe exudative dermatitis of the face (Figs. 238, 239), neck, and hands (Fig. 240, 241). Tests for photosensitivity showed an exudative dermatitic reaction four hours after exposure to ultraviolet light at a distance of 50 cm. for 20 seconds and to direct sunlight for 1 minute.

While examination of the urine for porphyrin was negative, the stool was strongly positive by fluorescent microscopy and also by spectroscopy. The galactose tolerance test for liver function was normal, but the glycocoll (glycine) tolerance test revealed marked impairment of hepatic function, the figures being as follows: fasting 8 mg. per cent, peak after 25 Gm. of glycocoll 14 mg. per cent (an increase of 75 per cent) and after three hours, when the original fasting level should have been reached, 12.2 mg. per cent. The patient was put on a strict sugar-water diet for four days, with the result that the fecal porphyrin disappeared completely. Simultaneously the clinical manifestations improved markedly; however, it should be emphasized that at the same time the patient was in a completely darkened room. A diet consisting solely of vegetables was then instituted for six days, at the end of which period the stool was still free of porphyrin. At this point the patient was given moderate amounts of boiled beef, with the result that in thirty-six hours por-

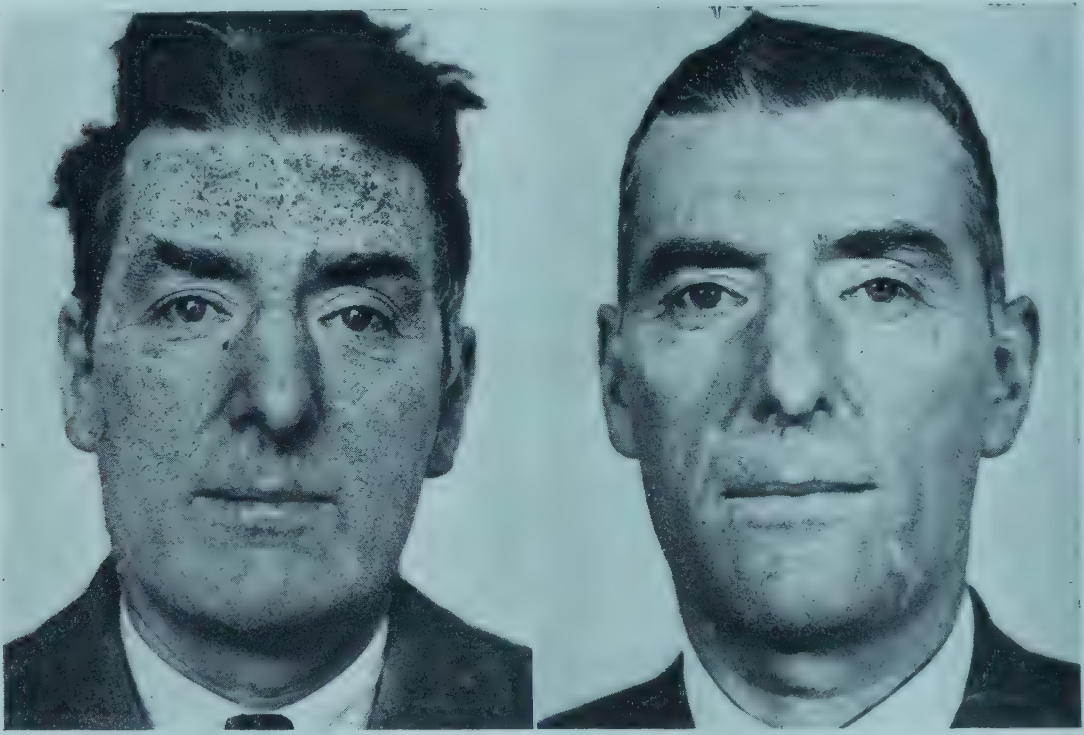


Fig. 238 Fig. 239

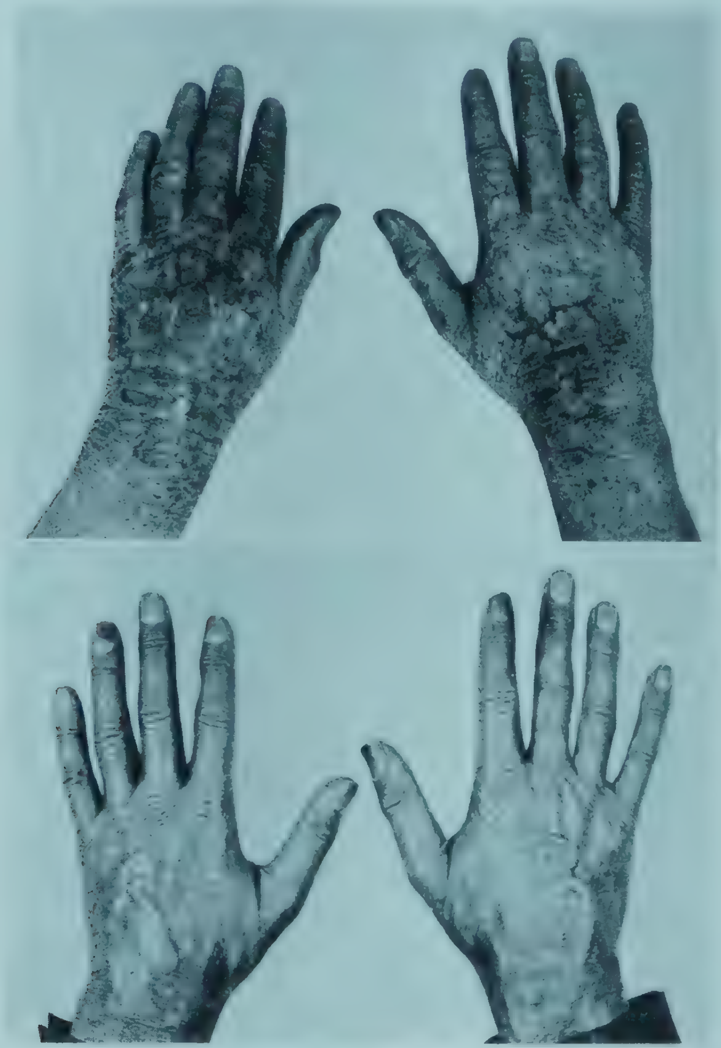
Chronic Dermatitis Due to Light Hypersensitiveness on the Basis of Hepatopathy, Intestinal Dysbacteria, and Porphyrinopathy

Fig. 238. Before treatment.

Fig. 239. After several weeks of treatment with viable B. coli by mouth plus injections of crude liver extract.

phyrin reappeared in the stool, although in smaller amounts than formerly. Return to a vegetarian regimen again caused porphyrin to disappear after eight days. Later on, eggs, fish, and milk were successfully added, all of which produced traces of fecal porphyrin.

Bacteriologic investigation of the stool showed that when the patient partook of a normal dietary and the stool contained an abundance of porphyrin, the intestinal flora was characterized by B. coli whose cultural and staining properties were atypical and, in addition, by the presence of large numbers of streptococci and yeasts. By excluding food containing animal protein a decrease in streptococci and yeasts was achieved, but there was no change in the characteristics of the atypical B. coli. Therapy with a viable culture of normal B. coli (Mutaflor) for eight weeks, in order to correct the dysbacteria, plus continuance of the animal protein–free diet accom-



Chronic Dermatitis of Hands Due to Light Hypersensitiveness

Fig. 240. (upper) Before treatment.

Fig. 241. (lower) After several weeks of treatment with viable B. coli by mouth plus injections of crude liver extract.

plished the establishment of the normal strain of B. coli. In addition the patient was given 3 cc. of crude liver extract by intramuscular injection every second day. This combined therapy accomplished (1) a marked decrease of the light sensitiveness, so that the patient could tolerate daylight but not direct sunlight without experiencing skin manifestations; (2) disappearance of fecal porphyrin on a normal diet; (3) improvement in the liver function as shown by the glycocoll tolerance test, the figures now being: fasting 7.2 mg. per cent, peak after 25 Gm. of glycocoll 10 mg. per cent (an increase of only 39 per cent) and after three hours 8.7 mg. per cent. Despite the dietary restriction, the patient had gained 12 pounds.

Case 2. A 52 year old woman had had infantile dermatitis in childhood, since when she had almost continuously had a slight dermatitis on the basis of a rather marked ichthyosis. In the course of her first pregnancy, at the age of 22, the patient had jaundice for about one month, but this did not appear during two subsequent pregnancies. Following exposure to sunlight during a cruise, a severe inflammation developed on the exposed parts of the body. A diseased gallbladder, which was thought to be the cause, was removed. Some months later the dermatosis recurred on the face, neck, and extremities after exposure to sunlight at the seashore for a short time.

In addition to the jaundice mentioned above, the fact that the patient had indulged freely in "social drinks" for many years raised the suspicion of the presence of hepatic disease.

On admission to the hospital the patient exhibited a severe, partly oozing dermatitis on the uncovered areas. The rest of the skin was markedly ichthyotic. After three days on a meat-free diet a hydrochloric acid extract of the urine gave strong fluorescence under ultraviolet light and showed spectroscopic bands characteristic of porphyrin. An ether extract of the stool exhibited marked fluorescence and porphyrin bands, while the hydrochloric extract presented moderate fluorescence and faint bands.

Bacteriology of the stool revealed in addition to normal B. coli the presence of hemolytic B. coli, Streptococcus viridans, and Streptococcus hemolyticus. The bromsulfalein excretion test indicated impairment of hepatic function, in that there was 25 per cent retention of the dye. The treatment consisted of a diet free of animal protein and animal and vegetable fat, but high in vegetables, fruits, and carbohydrates, injections of 3 cc. of crude liver extract every second day, nicotinamide 100 mg. three times a day, riboflavin 5 mg. daily, yeast concentrate 2 tablets three times a day, and B. acidophilus whey culture 1 tablespoonful with 1 tablespoonful of lactose three times a day. In addition the patient was kept in a totally darkened room and received 10 units of regular insulin three times daily.

The dermatitic skin manifestations subsided entirely in about five days. However, it was only after one month of the regimen described above that the porphyrin disappeared completely from the stool and the urine. At this time the liver function was normal, as evidenced by the absence of bromsulfalein retention. In the stool the hemolytic B. coli and the streptococci had disappeared. However, when protein hydrolysates or milk or cheese were added to the diet, small amounts of porphyrin reappeared in the urine and the stool. At the same time moderate numbers of streptococci were found in the stool culture. Porphyrin and the streptococci were further slightly increased when meat was allowed. Nevertheless, the patient could now tolerate exposure to normal daylight with impunity. The pathologic flora and the fecal porphyrin were temporarily controlled by oral administration of penicillin (20, 000 units eight times a day for about two weeks).

A number of pertinent questions regarding the relationship between light hypersensitiveness and porphyrinopathy, hepatopathy, and dysbacteria still remain unanswered. What is the nature of the substances from which the porphyrins are derived in these cases? Which type or types of porphyrin have the capacity to sensitize? Is it the pathologic intestinal flora that forms porphyrin from ingested animal protein? What role, if any, does hepatic disease play in the formation of pathologic porphyrins? Moreover, is porphyrin actually the underlying cause of actinic dermatoses? This last question is even more controversial today than it was some years ago. Some authors now go so far as to deny the etiologic importance of porphyrins, holding that they are formed as a consequence of the destruction of skin tissue incidental to severe reactions to light. Regardless of all these more or less theoretical questions, the fact remains that in a considerable percentage of light dermatoses the dietary regimen described above, plus liver therapy and correction of the pathologic intestinal flora, has achieved excellent therapeutic results in the hands of the present writer.

Since we cannot undertake to present an exhaustive consideration of these problems here, we refer the interested reader to the excellent monographs contributed by Blum[1189] and Dobriner and Rhoads.[1190] The subject is discussed in this volume on page 335.

The following protective ointment is recommended for local application:

		Gm. or Cc.	
℞	Nutracolor	2.0	ʒss
	Titanium oxide	15.0	℥ss
	Bentonite	2.5	gr XL
	Glycerin	15.0	℥ss
	Aqua rosae	q.s. ad 100.0	q.s. ad ℥iii

1189. Blum, H. F.: Photodynamic Action and Diseases Caused by Light. New York: Reinhold, 1941.
1190. Dobriner, K. and Rhoads, C. P.: Physiol. Rev. **20:** 416, 1940.

CHAPTER XVII

Pemphigus and Associated Diseases

We are not yet in a position to apply etiotropic therapy in pemphigus vulgaris and dermatitis herpetiformis of Duhring (although we[1191] have good reason to believe that these dermatoses are caused by virus), so we must do everything possible to combat the most severe and menacing symptom of pemphigus, namely, the abnormally high rate of protein disintegration which leads to cachexia. That foods may be an etiologic factor in dermatitis herpetiformis is indicated by the observation of Sammis,[1191a] who described a case in which the lesions appeared after the ingestion of eggs, beef, fish, and cheese. Sutton[1191b] saw dermatitis herpetiformis develop in a child following the drinking of cow's milk. Thanks to the investigations carried out by Mulvehill[1192] and Prakken,[1193] we know that pemphigus patients regularly exhibit a low serum albumin level of 3.3 per cent or less, while the normal mean value is 4.6 per cent. On the basis of Stuewe's[1194] experimental work in the field of protein metabolism more than half a century ago, Herxheimer[1195] advocated that pemphigus patients be given a diet consisting largely of such protein-sparing substances as fats and carbohydrates. However, in view of the fact that these patients suffer acutely from loss of appetite, this type of dietary is hardly feasible. Moreover, it is now known that a high intake of carbohydrate and fat does not serve to protect against loss of protein in the serum (Weech[1196]). We have, in fact, become able to control hypoproteinemia with protein hydrolysates administered orally or, preferably, by the parenteral route if involvement of the mouth makes oral feeding difficult or impossible (see p. 121). Seeking for a method to cope with the disturbed protein metabolism in pemphigus in such a manner that the fats and carbohydrates in the ingested foods would be utilized first, while the protein would be stored, the writer tried a course consisting of administration of insulin and a diet high in carbohydrates and protein. Insulin seemed to be well suited for this purpose since, according to Lorant,[1197] it serves to encourage a positive nitrogen balance, even in nondiabetic individuals, and

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1191. Urbach, E. and Wolfram, S.: Arch. Dermat. & Syph. **33:** 788, 1936.
1191a. Sammis, F. E.: Arch. Dermat. & Syph. **32:** 798, 1935.
1191b. Sutton, R. L.: Am. J. M. Sc. **140:** 727, 1910.
1192. Mulvehill, W.: Arch. Dermat. & Syph. **49:** 327, 1944.
1193. Prakken, J. R.: Acta dermat.-venereol. **16:** 156, 1935.
1194. Stuewe, R.: Arch. f. Dermat. u. Syph. **36:** 191, 1896.
1195. Herxheimer, K.: Arch. f. Dermat. u. Syph. **36:** 141, 1896.
1196. Weech, A. A.: The Significance of the Albumin Fraction of Serum. (Harvey Lectures, 1937–1938). Baltimore: Williams & Wilkins, 1938.
1197. Lorant, J. S.: Wien. Arch. f. inn. Med. **9:** 409, 1925.

also improves the patient's appetite. In a number of cases this approach did indeed check the loss of weight and stimulate the desire for food to such an extent that a high caloric diet could be administered. Subjectively, the patients felt better; objectively, however, the showers of blisters and the fever naturally failed to respond. Martenstein[1198] also achieved some improvement with a combination of insulin and a fattening diet plus Stovarsol or Plasmochin.

The extensive work done in this field during the past years has revealed that the showers of blisters in pemphigus and dermatitis herpetiformis Duhring are regularly accompanied by a disturbance of the sodium chloride metabolism. Thus, the writer[32] demonstrated by chemical analysis of the tissues that sodium chloride is retained in the skin of pemphigus patients. While Kartamischew[1199] is of the opinion that pemphigus is primarily due to this metabolic disturbance, we feel that the abnormal chloride metabolism is only a secondary manifestation which accompanies every severe general disease—e.g., cachexia due to malignancy, chronic nephritis, and chlorosis. Furthermore, the writer has set up the working hypothesis that sodium chloride is able to give some degree of protection against the consequences of the greatly accelerated breakdown of protein. Elsewhere we[32] have presented a review of the literature on which we base our view that administration of sodium chloride can check the destruction of tissue protein by forming loosely bound salt-protein combinations. It is known that a pronounced deficiency of salt leads to pathologic proteolytic processes in the body. This is generally the result of dehydration due to a lack of sodium. In addition, however, it seems likely that salt deprivation exerts a direct influence on protein metabolism. Thus, Urbach and Schnitzler[1200] obtained good therapeutic results with salt in cases of roentgen sickness, a condition which is characterized by destruction of protein as evidenced by an increase in the total and nonprotein nitrogen both in the blood and the skin. These various findings led us to administer small quantities of salt, 3 to 5 Gm. daily in divided doses, some being mixed with the food and some of it given in wafers, to pemphigus patients. We feel that this treatment was followed by temporary improvement in a number of cases. Stuempke[1201] has reported a similar response to physiologic salt solution given by mouth. We are, of course, fully aware of the fact that these measures actually constitute only symptomatic therapy. However, in addition to the fact that sodium chloride, by combining with some tissue proteins, presumably provides a form of defense reaction on the part of the organism in its effort to check

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1198. Martenstein, H.: Zentralbl. f. Haut- u. Geschlechtskr. **36:** 707, 1931.
1199. Kartamischew, A.: Arch. f. Dermat. u. Syph. **143:** 184, 1923.
1200. Urbach. E. and Schnitzler, H.: Klin. Wchnschr. **8:** 2179, 1929.
1201. Stuempke, G.: Med. Klin. **19:** 1044, 1923; **20:** 1007, 1924.

excessive destruction of protein, it seems logical to administer it in order to prevent salt depletion consequent to the constant oozing of fluids from extensively denuded surfaces.

While the writer,[32] Koenigstein,[1202] Tanimura,[1203] and other authors have seen showers of blisters make their appearance following institution of an extremely salt-poor diet, many others have observed cases which showed marked improvement on the low salt diet of Sauerbruch and Herrmannsdorfer. Favorable responses to the latter dietary measure have been reported by Arzt,[1204] Baum,[1205] Doerffel,[71] Stuempke and Mohrmann,[991] and others. Another group of authors, including Volk, Riehl, Jr., Musger, and the present writer, failed to note improvement on the salt-poor diet. Nor did we note any response to a starvation diet, as recommended by Noltenius.[1206] In fact, the writer is in a position to state categorically that a starvation diet serves only to hasten the decline of the patient, who is already in an undernourished state, and is therefore definitely contraindicated.

It is interesting to note Werther's[1207] allegation that Burgundy wine is capable of provoking new showers of blisters in pemphigus. This may be explained by the fact that this wine contains minute quantities of iodine; for, as others and ourselves[1208] have demonstrated, every one of the halogens, but particularly iodine, is capable of eliciting showers of blisters in pemphigus.

Vitamin D in massive doses (300,000 to 400,000 units daily) has been recommended by Ludy and Devalin,[1209] Tauber and Clarke,[528] and King and Hamilton.[1210] Ebert[442] states that while he has seen remissions in some cases, the improvement is only temporary and vitamin D is rarely of any value in the subsequent exacerbation. He knows of no instance in which vitamin D has led to great improvement. Our own observations coincide completely with Ebert's findings.

In summary, we suggest that in addition to chemotherapy pemphigus patients be given a diet high in calories and vitamins. Should a patient be unable to take enough food, protein hydrolysates, either orally or parenterally, are indicated. In addition, sodium chloride 1 Gm. in enteric-coated tablets three times a day should be tried. Furthermore, insulin should be administered in order to enhance the appetite.

1202. KOENIGSTEIN, H.: personal communication.
1203. TANIMURA, C.: Jap. J. Dermat. & Urol. **39:** 85, 1936.
1204. ARZT, L.: Wien. klin. Wchnschr. **43:** 696, 1930.
1205. BAUM: in discussion to LANGER: Zentralbl. f. Haut. u. Geschlechtskr. **33:** 301, 1930.
1206. NOLTENIUS, F.: Arch. f. Verdauungskr. **49:** 43, 1931.
1207. WERTHER: Zentralbl. f. Haut- u. Geschlechtskr. **34:** 138, 1930.
1208. URBACH, E.: Zentralbl. f. Haut- u. Geschlechtskr. **33:** 672, 1930.
1209 LUDY, J. B. and DEVALIN, C. M.: Urol. & Cutan. Rev. **36:** 817, 1932.
1210. KING, H. and HAMILTON, C. M.: Arch. Dermat. & Syph. **39:** 515, 1939.

CHAPTER XVIII

Pyogenic Infections of the Skin

THE most important pyogenic dermatoses are furuncles, carbuncles, sycosis coccogenica, sycosis nuchae, hidrosadenitis, granuloma pyogenicum, pemphigus neonatorum, onychia, and paronychia.

In every case of refractory furunculosis or of any other cutaneous pyogenic infection, particularly when the condition is recurrent, the physician should consider the possibility of diabetes. It is unfortunately still the practice in many instances to rely on the fasting blood sugar in order to determine whether the patient has a disturbed sugar tolerance. In Part One of this book we stressed the importance of the sugar tolerance test in every suspicious case. Furthermore, Urbach and Sicher[1211] have pointed out that in occasional cases the disturbance in the carbohydrate metabolism is confined to the tissues and under these circumstances is not necessarily reflected in the blood sugar curve. In a series of experimental-chemical studies, Urbach and Lentz[11] have shown that the tissues of the skin constitute an excellent storage place for carbohydrates but that their sugar content can be considerably decreased by a carbohydrate-free diet plus insulin. The following representative case may serve to illustrate this point:

A man, 49 years of age, had been suffering for five years with severe, constantly recurrent furunculosis (Fig. 242). During this period, he had been obliged to seek hospital treatment ten times (in three different hospitals). In view of the fact that the patient was very obese and his complexion was purplish red, blood sugar tolerance tests were repeatedly made; but since these were consistently normal, it seemed impossible to make a diagnosis of diabetes. When we performed the sugar tolerance test, we found a nearly normal curve (97, 164, 164, 139, 97 mg. per cent), but examination of the skin sugar, on the other hand, revealed the high fasting level of 81 mg. per cent. We refrained from performing a complete skin sugar tolerance test in this case because of the danger of infection presented by the severe furunculosis. The patient was put on a strict diabetic diet and was given 10 units of insulin three times daily. By the end of the eighth day the furuncles had vanished completely, without any kind of local therapy. Thereupon, by way of an experiment, the patient was put on a diet free of salt, but including average amounts of carbohydrates. This had to be stopped after the third day because of the reappearance of furuncles. Strict adherence to a diabetic diet plus 30 units of insulin daily again served to clear up the condition, and the patient suffered no further attacks during the subsequent seven days, when he was on a very low carbohydrate diet. Then he was again given a salt-free diet of ordinary carbohydrate content, and again this had to be stopped after four days because of the reappearance of furuncles. Subsequently, throughout the months that the patient was kept under observation, a very low carbohydrate diet kept him free of all clinical manifestations without the use of insulin.

[1211] URBACH, E. and SICHER, G.: Arch. ch. f. Dermat. u. Syph. **157:** 160, 1929.

Since it is sometimes not feasible to perform a sugar tolerance test, we recommend trying a strict diabetic diet for a week or so in every case of refractory furunculosis, pyodermia, and above all in cases with sweat-gland abscesses, in adults and children alike. A surprisingly high percentage of these cases will respond to this dietary therapy; moreover, even in cases where no disturbed tolerance for carbohydrates is involved, the nonspecific reaction of the organism as a whole—that is, its alterative response to the abrupt change in diet—exerts a beneficial influence, both generally and locally, and thus acts as an adjuvant therapeutic factor.

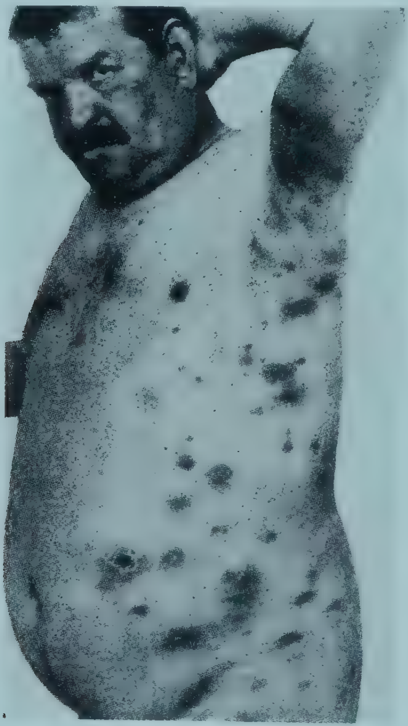

FIG. 242. CHRONIC FURUNCULOSIS ON THE BASIS OF SKIN DIABETES

A 49 year old obese man with chronic recurrent furunculosis of five years' duration. Blood sugar tolerance curves were repeatedly normal. Skin sugar level, however, was high (87 mg. per cent). Diabetic diet plus insulin quickly caused involution of the lesions. Return to normal diet and discontinuance of insulin caused recurrence of furunculosis. Resumption of dietary regimen again controlled the cutaneous infection.

Other authors are of the opinion that the quantity of carbohydrates in the diet is of no consequence. In view of the fact that this question is still so highly controversial, we shall present a brief summary of some of the present views on the subject of the influence of carbohydrate on pyogenic dermatoses. According to Stokes, Beerman, and Ingraham,[174] the influence of carbohydrates on inflammatory conditions of the skin seems to take a threefold direction. First, their effects may be exerted through the gastrointestinal tract, where intestinal intolerance for carbohydrates may produce a pathologic picture leading to vasomotor instability and localized vasodilatation, e.g., on the face, on which terrain infective processes readily take root. Second, Pillsbury and Sternberg[163] have presented experimental evidence that infective cutaneous processes are profoundly influenced by hydration, and they pointed to the fact that a high carbohydrate intake promotes water retention in the tissue. And, as Kulchar and Alderson[178] have stressed, carbohydrate restriction leads to dehydration, followed by retrogression of the inflammatory manifestations associated with the infection. Third, Pillsbury[1212] has demonstrated that the high carbohydrate content of the tissues influences inflammatory processes through the formation of lactic acid as a sequel to the local inflammation, and that the formation of lactic acid leads to a marked change in the cellular and leukocytic reaction, coincident with the shift in pH.

On the other hand, Rudy and Hoffman[224] believe that the skin manifestations in diabetes mellitus are not related to the hyperglycemia but are attributable to heightened vulnerability of the skin resulting from a deficiency of the components of the vitamin B complex. According to Gross,[843] the danger of an excessive carbohydrate intake lies in the well established fact that sugar and refined flour are lacking in vitamins. Thus, a diet high in carbohydrate will reduce the intake of natural cereals, with their vitamin B complex. Moreover, its increase in the diet actually steps up the requirements for vitamins, particularly those of the water-soluble group. In this connection it is interesting to recall the century-old custom of treating furunculosis with fresh yeast, orally, an approach with which the present writer as well as Barber[1213] has obtained good results. In a series of animal experiments Pfannenstiel and Scharlan[1214] demonstrated that staphylococcic skin infections can be effectively combated by a diet rich in vitamin B complex. Sutton[841] has reported good results with a liver diet in cases of chronic furunculosis; and others have been equally successful with liver injections.

In the light of our present understanding, we can recommend the following practical dietotherapeutic approach. If the blood sugar tolerance test indicates a reduced carbohydrate tolerance, a diabetic regimen should be instituted and continued for a reasonable period of time; in chronic cases where the blood sugar tolerance curve is normal and where skin sugar determination is not feasible, there is also good reason to try a diabetic diet; then, if no clinical response is observed, vitamin therapy, in-

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1212. Pillsbury, D. M.: J. A. M. A. **96:** 426, 1931.
1213. Barber, H. W.: Guy's Hosp. Rep. **80:** 152, 1930.
1214. Pfannenstiel, W. and Scharlan, B.: Ztschr. f. exper. Med. **71:** 465, 1930.

cluding injections of crude liver extract, fresh yeast (orally), and niacin, should be administered.

Callaway and co-workers[1117] found the vitamin A and C levels to be significantly low in a group of pyodermia cases. These authors believe that the reserves of vitamins are more rapidly depleted in pyogenic infections of the skin than in other dermatoses, and they feel, therefore, that the administration of vitamins A and C is indicated.

The present writer has been able to trace an occasional case of chronic furunculosis to intestinal dysbacteria. Correction of the pathologic intestinal flora by the use of Mutaflor or some of the other measures outlined on page 321 served to control the cutaneous infection completely (Fig. 243).

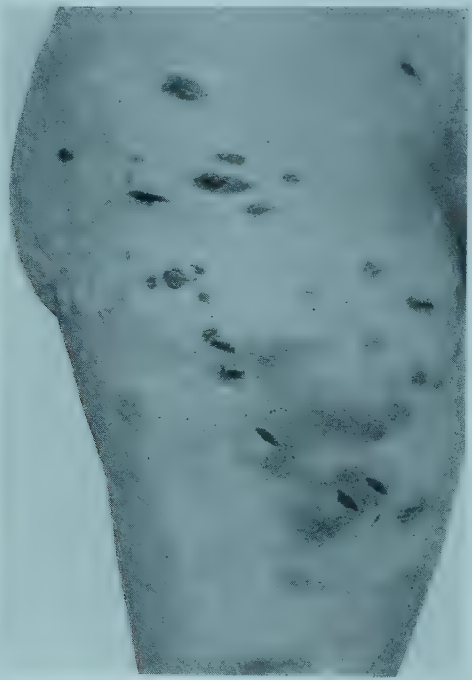

FIG. 243. MULTIPLE CUTANEOUS ABSCESSES DUE TO B. COLI INFECTION

Schwartzman et al.[1215] described a severe case of dermatitis exfoliativa neonatorum (Ritter's disease) which, in all probability, is identical with impetigo bullosa due to staphylococcus infection (Zakon,[1216] Sutton and Sutton[337]). The infant, 1 month of age, had been fed a formula of boiled whole milk without orange juice or cod liver oil since birth. While vitamin B complex therapy was of no avail, the child made a complete recovery within a few days on treatment consisting of riboflavin 2 mg. three times a

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1215. SCHWARTZMAN, J., DRAGUTSKY, D., and ROOK, G.: Am. J. Dis. Child. **62:** 352, 1941
1216. ZAKON, S. J.: Arch. Dermat. & Syph. **24:** 830, 1931.

day plus a 50 per cent mixture of cod liver oil U.S.P. in a base of petrolatum and paraffin applied locally.

Lastly, mention should be made of an inflammatory and suppurative disorder of the eccrine sweat glands, a condition which is very common in China and has been described by Reiss[1217] as syringadenitis suppurativa tropicalis. Reiss has advanced evidence that this condition is furthered by excessive loss of vitamin C and a disturbance of the carbohydrate metabolism. Treatment consists of vitamin C in large doses (1,000 mg. daily) and appropriate topical applications.

[1217] Reiss, F.: J. Lab. & Clin. Med. 28: 1082, 1943.

CHAPTER XIX

Cutaneous Tuberculosis

MUCH credit is unquestionably due Gerson[198] as well as Sauerbruch and Herrmannsdorfer[16] for valuable contributions to the therapy of cutaneous tuberculosis in the form of the diets which bear their names. Although over a hundred and thirty years ago Struwe advocated a salt-poor diet for the treatment of tuberculosis, it was Gerson who really introduced dietotherapy for cutaneous tuberculosis and who methodically studied the clinical course of the disease under the salt-poor, high vitamin dietary he had planned. Sauerbruch and Herrmannsdorfer continued these investigations on more extensive material and introduced some minor modifications of Gerson's original diet. Therefore, as discussed at some length on page 65, we are now in possession of two dietary procedures which are not quite identical, but which have in common the restriction of the intake of table salt, the requirement of great quantities of vitamin-rich, fresh vegetables, and a change in the proportionate composition of the diet with regard to protein, fat, and carbohydrates.

This dietary therapy for cutaneous tuberculosis has been extensively tested and approved by the majority of authors (Jesionek,[1218] Jesionek and Bernhardt,[1219] Bommer,[181] Volk,[1169] Wichmann,[1220] Jadassohn,[1221] Stuempke and Mohrmann,[991] Brunsgaard,[1222] Scolari,[183] Dundas-Grant,[1223] Stokes,[272] and others. Particularly noteworthy are the investigations which Jacobson and Brill[1224] and Gawalowski[1225] carried out over a number of years on extensive material. The Russian authors treated 124 patients who were under observation for five years, while the Czechoslovak investigator followed 127 cases. Both groups showed marked improvement. Interesting, too, is the report submitted by Simon and Kaplanskaja[1226] which shows the necessity for adhering to the salt-poor diet for an adequate period of time (Table 86). The following six illustrations, which the late Dr. Volk was kind enough to place at the writer's disposal, will give the reader a clear picture of the manner in which cases of lupus vulgaris responded clinically to dietary treatment alone (Figs. 244–251).

1218. JESIONEK, A.: München. med. Wchnschr. **76:** 867, 1929.
1219. JESIONEK, A. and BERNHARDT, L.: Diätetische Behandlung der Hauttuberkulose und Ernährungsbiologie. (Tuberkulose-Bibliothek, no. 37), Barth, 1930.
1220. WICHMANN, P.: Klin. Wchnschr. **8:** 2366, 1929.
1221. JADASSOHN, W.: Delib. 8th Internat. Dermat. Congress p. 479, 1930.
1222. BRUUSGAARD, E.: Acta dermat.-venereol. **13:** 628, 1932.
1223. DUNDAS-GRANT, J.: Practitioner **132:** 101, 1934.
1224. JACOBSON, A. and BRILL, M.: Sovet. vestnik. venereol. i. dermat. no. **3:** p. 11, 1938.
1225. GAWALOWSKI, K.: Česka Dermat. **18:** 59, 1938.
1226. SIMON, L. and KAPLANSKAJA, S.: Sovet. vestnik. venerol. i. dermat. **12:** 1107, 1936.

However, we must not fail to mention several dissenting opinions. These do not deny that the diet can exert a favorable influence; they are concerned, in part, with those forms of cutaneous tuberculosis which are amenable to the dietotherapeutic approach and, in part, with the precise manner in which the diet exerts its influence. Although a number of competent observers have emphasized the point that lupus could be com-

TABLE 86.—*Effect of the Time Factor on the Influence of a Low Salt Diet on Skin Tuberculosis (Simon and Kaplanskaja*[1226]*)*

Degree of Recovery	After 1½–2 mo.	After 3–4 mo.	After 5–6 mo.	After 7–8 mo.	After 10–12 mo.	Total
Full recovery	—	—	5	5	1	11
Marked improvement	7	7	4	8	4	30
Improvement	5	3	2	—	1	11
No change	3	—	—	—	—	3
Total	15	10	11	13	6	55

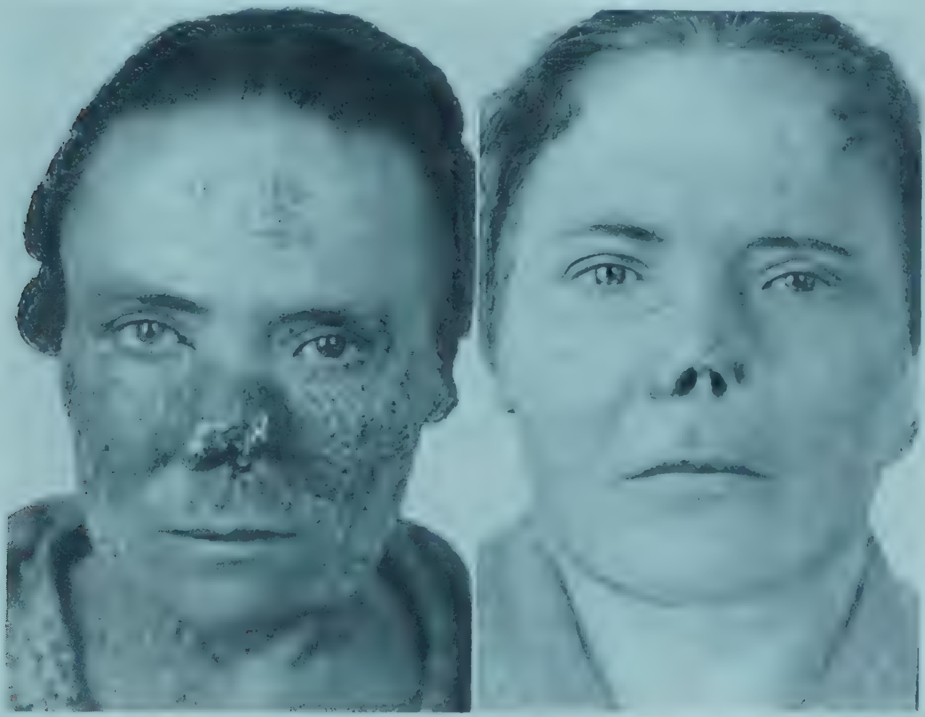

FIG. 244 FIG. 245

EFFECT OF SAUERBRUCH-HERRMANNSDORFER DIET ON LUPUS VULGARIS

FIG. 244. Before therapy.

FIG. 245. After nine months of exclusive dietotherapy.

(Courtesy of Dr. R. Volk.)

pletely cured by dietary therapy alone, experience (notably that of Volk and of Jesionek) has shown that, at least with regard to the time element, quicker results can be obtained with a combination of the old, tried method of general measures plus irradiation and local treatment, in addition to the low salt diet.

Most observers state that the best results can be achieved with the low salt diet in the ulcerative, tumid, and hypertrophic forms of lupus. Some even declare that flat lupus nodules will actually disappear. In addition, there are numerous reports of the therapeutic efficacy of the low salt diet in other forms of cutaneous tuberculosis. For example, Kerl[1227] reported a case with indolent tuberculous ulcers which had stubbornly resisted all other therapy but which was completely cured by this dietary measure, on which the patient also gained considerable weight (16 Kg.). There are also observations by Blumenthal et al.[1147] on the beneficial effect of this diet on tuberculosis ulcerosa miliaris and one by Volk[1169]

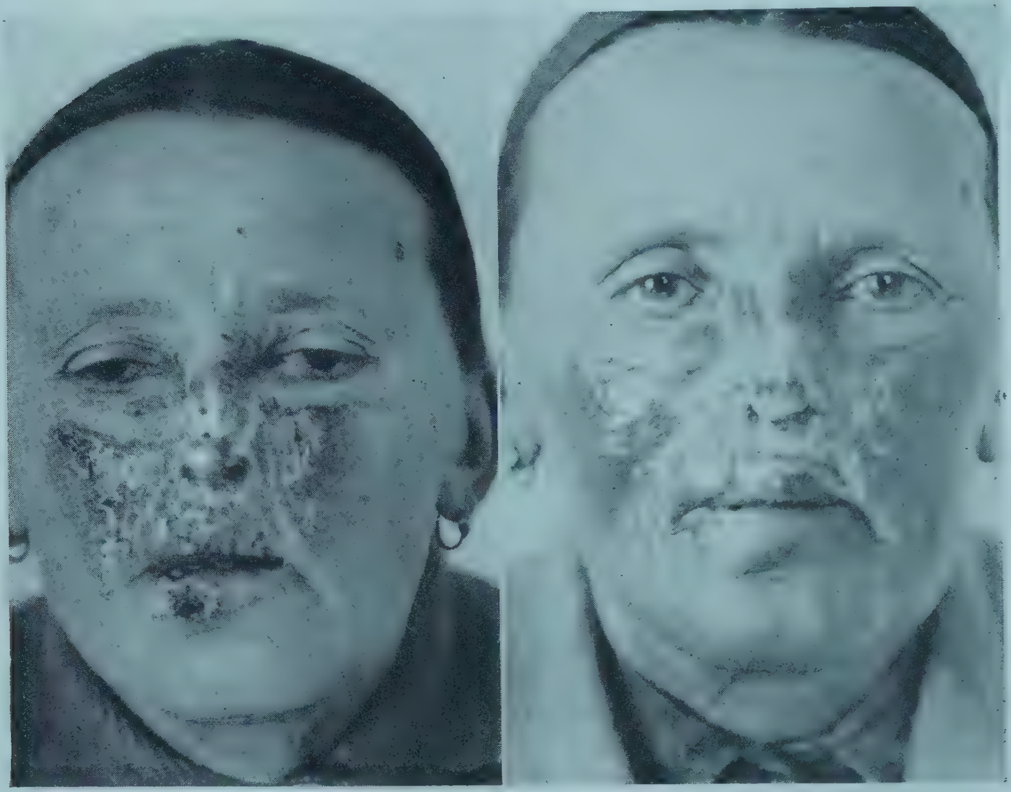

FIG. 246 FIG. 247

EFFECT OF SAUERBRUCH-HERRMANNSDOFER DIET ON LUPUS VULGARIS

FIG. 246. Before therapy.

FIG. 247. After ten months of exclusive dietotherapy.

(Courtesy of Dr. R. Volk.)

[1227] KERL, W.: Zentralbl. f. Haut- u. Geschlechtskr. **34:** 29, 1930.

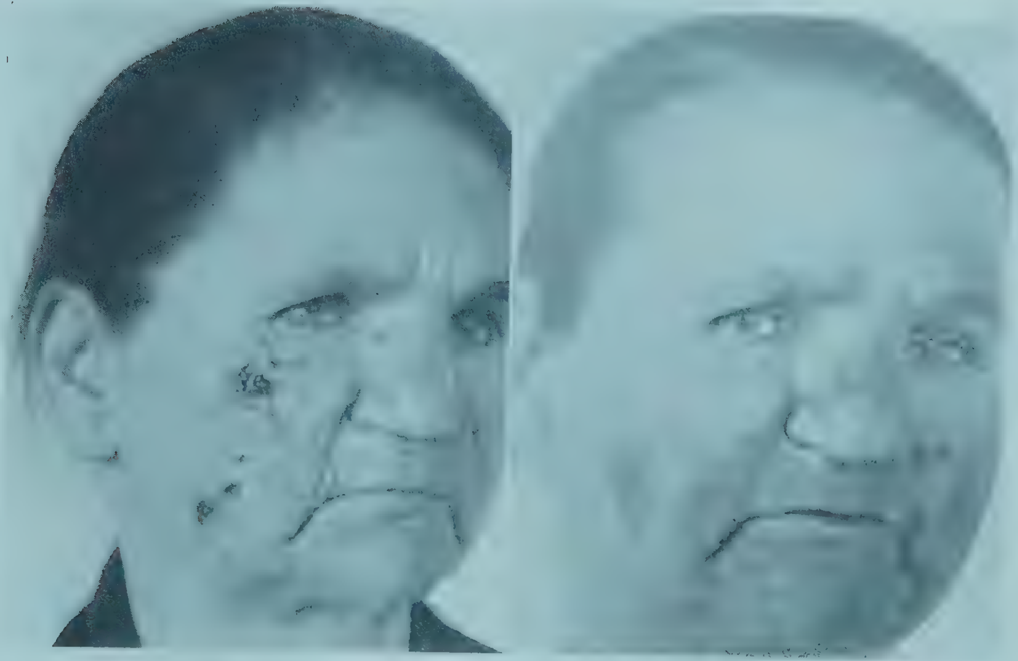

Fig. 248 Fig. 249

Effect of Sauerbruch-Herrmannsdorfer Diet on Lupus Vulgaris

Fig. 248. Before therapy.

Fig. 249. After nine months of exclusive dietotherapy.
(Courtesy of Dr. R. Volk.)

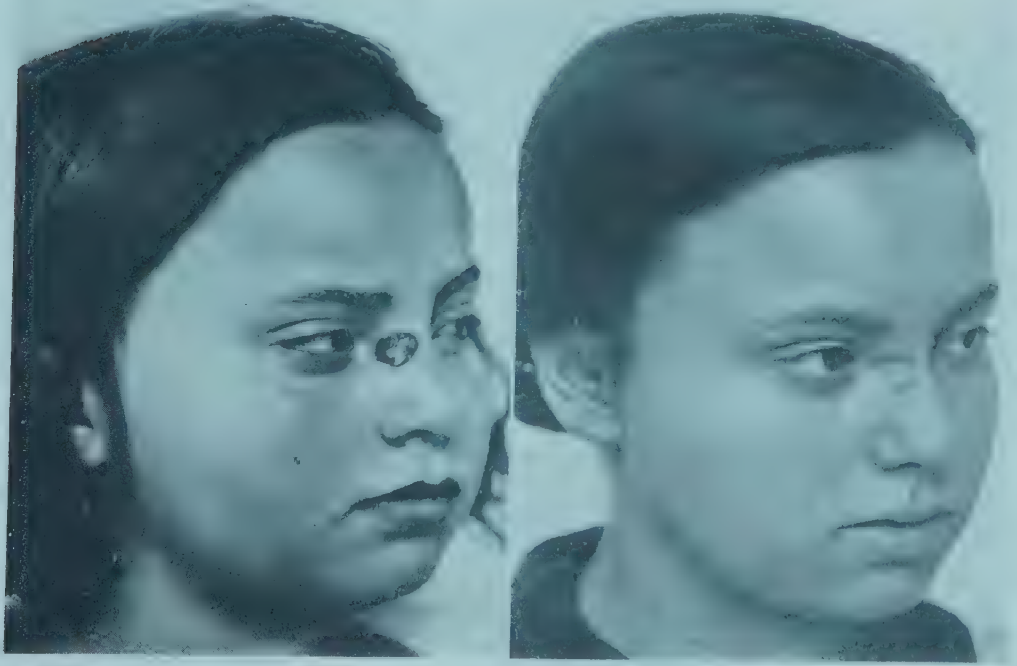

Fig. 250 Fig. 251

Effect of Sauerbruch-Herrmannsdorfer Diet on Tuberculous Ulcer

Fig. 250. Before therapy.

Fig. 251. After six months of exclusive dietotherpy.

on tuberculosis of the mucosa, involving particularly the hard and soft palate and the upper respiratory tract; a report by Rusch[1228] and one by Volk[1169] of its efficacy in tuberculids and in erythema induratum Bazin; and one by Axmann[1229] of good results obtained in tuberculous fistulas. On the other hand, it has been observed that tuberculosis cutis colliquativa and tuberculosis verrucosa cutis respond only moderately well to this treatment and that the response is far from satisfactory in tuberculosis miliaris of the tongue, lips, and gums, as well as in lupus of the nasal mucosa (Volk[1169]). Gans,[1230] Wichmann,[1220] and others were unable to achieve a complete cure of lupus with dietary treatment alone, nor could they prevent recurrences with this method. Wichmann[1220] feels that the flat, dry nodules of lupus do not disappear completely. However, he, too, stresses the splendid therapeutic results which can never be achieved with ordinary dietary methods.

There is great divergence of opinion as to the nature of the mechanism by which the low salt diet exerts its influence. It was originally believed that the improvement should be attributed to the lack of table salt, which tends to counteract the swelling characteristic of inflammatory conditions by depleting the cutaneous salt deposits and thus leading to a decrease in exudative processes in the skin. Other observers, such as Kroetz,[141] are of the opinion that the low salt diet leads to changes in the relative amounts of minerals stored in the tissues, reflected notably by a rise in the calcium level in the blood. Falta[1231] explains the good effect of the diet by the fact that it is poor in sodium and rich in potassium and thus strongly promotes a decrease in the intercellular fluids. Herrmannsdorfer[161] and Doerffel[71] ascribe the efficacy of the diet, which in their opinion exerts an acidotic influence, to its ability to acidify the tissues. This view is contradicted by a number of authors, including Straub,[142] Kroetz,[141] and von Noorden.[172] According to Bommer,[181] the successes achieved with this diet may be attributed to the fact that it serves to reduce and even cause disappearance of the excessive amounts of liquid in the edematous foci of lupus. As Bommer sees it, the Gerson diet exerts its influence primarily on the walls of the capillaries of the cutis, correcting the functional abnormalities of the capillary endothelium, which may be regarded as the basic cause of the edema. Furthermore, Bommer does not believe that the withdrawal of table salt alone is the chief reason for the diet's beneficial effect; he feels that this must be attributed to the combination of a minimum of salt with an abundance of vitamins.

[1228] Rusch: Zentralbl. f. Haut- u. Geschlechtskr. **34:** 409, 1930.

[1229] Axmann, H.: München. med. Wchnschr. **77:** 708, 1930.

[1230] Gans, O.: Delib. 8th Internat. Dermat. Congress. p. 460, 1930.

[1231] Falta, W.: Wien. klin. Wchnschr. **43:** 148, 1930.

In opposition to almost all other observers, Wichmann[1232] holds that the effectiveness of the diet is to be attributed, not to its drastic restriction of the table salt intake, but to the fact that it supplies an abundance of vitamins and fat, restricts the intake of carbohydrates, and prohibits excessive consumption of protein. We are indebted to Volk[1233] for an interesting and theoretically significant explanation of the action of the low salt diet in cutaneous tuberculosis. Volk assumes that the diet gives rise to genuine tuberculin reactions because the dietary therapy serves to destroy the tubercle bacilli in the lesions and the dead micro-organisms then elicit specific reactions in the diseased areas. According to Volk, this would explain the pronounced succulence and the exudation which occasionally takes place in these foci in patients treated by this method. Jesionek[1218] also believes that the low salt diet stimulates the immunizing factors of the skin.

According to Jesionek,[1218] Volk,[1169] Doerffel,[71] and a number of other observers who have treated a considerable number of cases of lupus with the Gerson or the Sauerbruch-Herrmannsdorfer diet alone, there are two distinct types of regressive changes. In one, the edematous swelling in the foci is reduced without any noteworthy reaction, and the livid color fades and is replaced by a more reddish halo around the nodules; this alone serves to flatten the entire lupus lesion. This process often begins a few days after institution of dietary therapy and is followed by depression of the individual lupus nodules, their borders becoming less distinct; as Bommer so aptly puts it, they seem to be "melting away." Lastly, the lesion is completely absorbed, leaving a light, atrophic scar. In the second type of regressive change involution is preceded by a more or less severe reaction. The focus becomes swollen, either wholly or in part, and when the reaction is particularly severe the lupus nodules even present necrosis here and there as well as pronounced crusting. After these manifestations have run their course, some of the infiltration will have disappeared completely, and the balance will have flattened out appreciably. The latter may reappear during the next reaction, but this need not necessarily occur, and the entire process may thenceforth continue in the less explosive manner of the first-mentioned type. The severe manifestations generally make their appearance somewhere between the tenth and fourteenth days following institution of dietary therapy but sometimes occur later and, in rare cases, earlier.

Scolari's[183] capillariscopic and electrothermometric investigations have revealed that the initial response to dietotherapy consists of circulatory

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1232. Wichmann, P.: Delib. 8th Internat. Dermat. Congress. p. 457. 1930.

1233. Volk, R.: Delib. 8th Internat. Dermat. Congress, p. 419, 1930.

stimulation in the lupus foci, partly through hyperemia, partly due to the formation of new capillaries.

When instituting the Gerson and Sauerbruch-Herrmannsdorfer diets, it is advisable, at least in the beginning, to hospitalize the patient in order to familiarize him with the principles and teach him the details of the therapy. Moreover, he should be helped to overcome his natural aversion to the salt-poor diet by showing him the progress made by other patients who have had the will power to adhere faithfully to the diet for some time. For it is impossible to achieve a complete and lasting cure by means of the salt-poor diet unless the patient is himself willing and able to carry out this regimen to the letter for months on end. It should be noted, however, that the meticulous execution of this dietary program depends not only on the patient's character and his determination to regain his health, but also on the proper method of preparing the food, since this alone will enable him to endure the diet. For detailed instructions in carrying out a salt-poor dietary, the reader is referred to Herrmannsdorfer[197] and Stern.[1234]

Instead of a low salt diet, Volk[202] tried a regimen low in carbohydrates and high in fat (50 to 60 Gm. carbohydrates, 60 to 80 Gm. protein, 200 Gm. fat, salt *ad libitum*) and reported satisfactory results. A word of warning is in order here, because such a diet sometimes elicits reactions so severe as to cause necrotizing inflammation of the affected areas. However, these will heal with good results. The rationale of this diet is, as Adlersberg and Porges[171] have pointed out, that it promotes dehydration in a similar manner and to the same extent as a low salt diet. Only recently Berke and Sandler[1235] reported the curative effects of a low carbohydrate, high protein regimen in tuberculosis.

Lastly, Gerson, Volk, and Doerffel recommend the interposition, at more or less regular intervals, of days on which the patient receives an entirely different form of diet, preferably one strictly limited to raw foods, a procedure which definitely seems to give a metabolic thrust to the entire organism. It appears to the present writer that the fact that entirely different forms of diets exert a therapeutic influence on cutaneous tuberculosis indicates that we are dealing once again with the effects of an "alteration" or *Umstimmung* diet (see p. 124). Such nonspecific heightening of the cutaneous defensive power achieved by dietary measures can, according to Doerffel,[1236] be effectively combined with specific local tuberculin therapy. The procedure is as follows. On three or four consecutive days 20 per cent tuberculin ointment is rubbed into the tuberculous focus

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1234. Stern, M.: Küchentechnische Anleitung zur Herstellung der kochsalzfreien Diät. Vienna: Deuticke, 1930.

1235. Sandler, B. P. and Berke, R.: Am. Rev. Tuberc. 46: 238, 1942.

1236. Doerffel, J.: Zentralbl. f. Haut- u. Geschlechtskr. 51: 327, 1935.

or applied in the form of tuberculin patches on sites previously prepared with 10 per cent salicylic acid in petrolatum. This is repeated three or four times at intervals of eight to fourteen days, depending on the intensity of the inflammatory reaction.

Charpy[1236a] employs large doses of vitamin D_2 and calcium gluconate in the treatment of tuberculosis of the skin. In 38 patients he prescribed 5 mg. of vitamin D_2 and 1 to 2 liters of milk daily or 0.5 Gm. of calcium gluconate by mouth twice daily. The patient is kept on a low salt diet. The course of treatment is generally 3 months. Charpy reports successful results in all cases.

Using Charpy's procedure, Gougerot and Gaullier[1236b] had only 3 failures in 21 cases treated. Degos[1236c] modified Charpy's technic, prescribing 3 doses of 15 mg. of vitamin D_2 during the first week, two doses during each of the second and third weeks, and then one dose weekly thereafter. The patient also takes 0.5 Gm. of calcium gluconate twice daily. The best results are obtained in lupus vulgaris, other forms of cutaneous tuberculosis responding poorly. The authors stress the use of chemically pure vitamin D_2 in alcoholic solution in order to avoid sclerosis, arterial calcification, or the possible toxic effects of large doses of vitamin D_2. Oily solutions are less effectual or are inactive.

1236a. CHARPY: Paris Letter, J.A.M.A. **129**: 1220, 1945.
1236b. GOUGEROT and GAULLIER: Paris Letter, J.A.M A. **129**: 1220, 1945.
1236c. DEGOS: Paris Letter, J.A.M.A. **129**: 1220, 1945.

CHAPTER XX

Lipoid Diseases of the Skin

CUTANEOUS lipoid diseases are caused by disturbances of the lipoid metabolism which lead to a flooding of the organism with the various types of lipoids; excessive storage of the latter in the skin gives rise to a number of different dermatoses. The most commonly encountered form is xanthoma, or xanthelasma, as we prefer to call it,[826] which is a result of a general or local disorder of the cholesterol metabolism (Figs. 252, 253).

Cutaneous and visceral deposits of lipoids can be induced experimentally in animals. Anitschkow[1237] placed rabbits on a diet containing large amounts of lecithin and observed typical xanthelasma lesions at skin sites which he had previously traumatized. In a like manner, Weidman[1238] was able to obtain similar lipid deposits in dogs. By feeding rabbits and hens cholesterol but without previous traumatization, Ishimaru[1239] was able to induce the accumulation of sudanophil doubly refractile bodies of cholesterol in the lymphatic channels of the skin. Schaaf,[1240] Nakanishi,[1241] Chuma,[1242] Weinhouse and Hirsch,[1243] and others noted that rabbits fed anhydrous lanolin developed hyperlipemia and typical xanthelasma with foam cells. Schaaf further observed that continued feeding of lanolin over a long period produced severe liver damage and that this brought about a characteristic shift in the concentration of the lipid fractions. The quotient of fixed cholesterol to phosphatide phosphorus was found to average 0.74 in normal rabbits and 1.53 in Schaaf's experimental rabbits. According to Schaaf, the latter figure corresponds to findings in xanthelasma in man. In addition to xanthelasma in the skin, lesions of this kind may also develop in the internal organs (e.g., the stomach, Borst,[1244] Kon[1245]).

The experimental work of Kon[1245] is particularly worthy of note. By feeding lanolin continually for a considerable period of time, this investigator was able to induce the development of an ichthyotic consistency of the skin, as well as mulberry-like keratosis and hyperkeratoses on the soles and the oral mucosa of rabbits. Experimental production of hyperkera-

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1237. ANITSCHKOW, N.: München. med. Wchnschr. **60:** 2555, 1913.
1238. WEIDMAN, F. D.: Arch. Dermat. & Syph. **15:** 659, 1927.
1239. ISHIMARU: Acta dermat. (Kioto) **1:** 389, 1923.
1240. SCHAAF, F.: J. Invest. Dermat. **1:** 11, 1938.
1241. NAKANISHI, M.: Jap. J. Dermat. & Urol. **33:** 48, 1933.
1242. CHUMA, M.: Virchow's Arch. f. path. Anat. **242:** 275, 1923.
1243. WEINHOUSE, S. and HIRSCH, E. F.: Arch. Path. **30:** 856, 1940.
1244. BORST, M.: Med. Klin. **19:** 1414, 1923.
1245. KON, Y.: Gann **11:** 29, 1917.

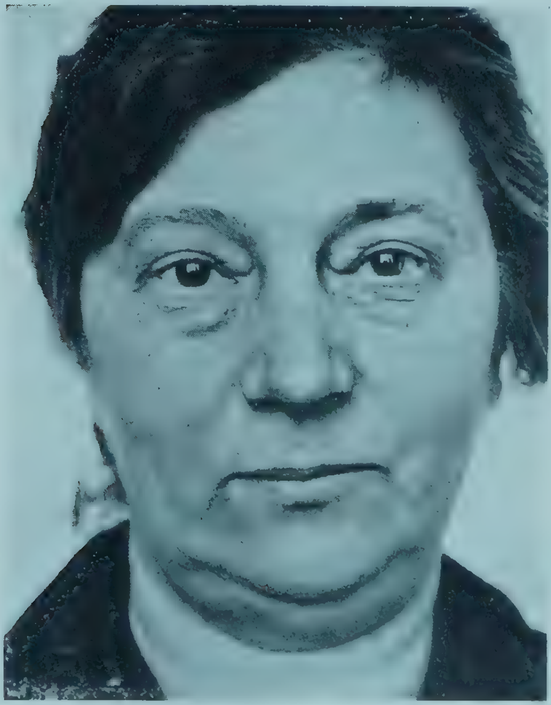

FIG. 252. XANTHELASMA PALPEBRARUM

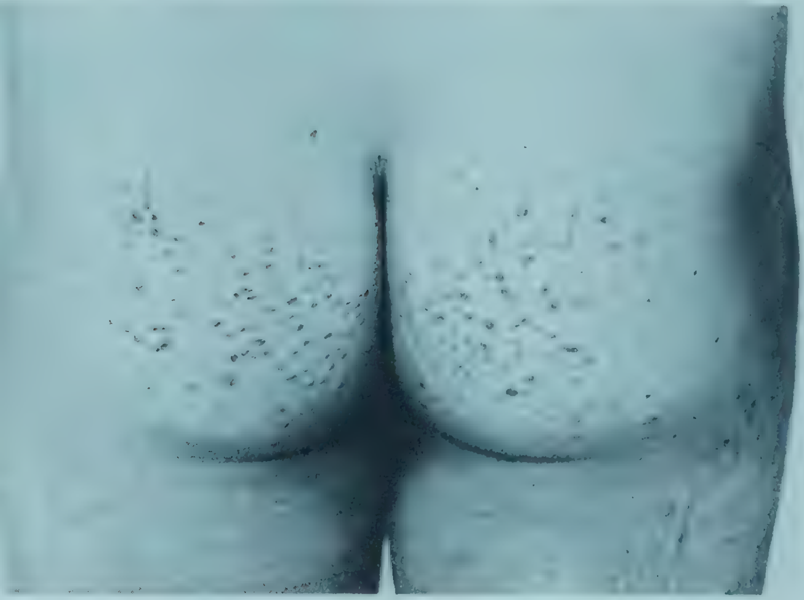

FIG. 253. XANTHELASMA PAPULOSUM

toses through an orally induced metabolic disorder is of special interest when considered in connection with certain lipoid dermatoses encountered in man, such as lipoidproteinosis and extracellular cholesterosis. The cutaneous changes produced by Kon correspond to the warty excrescences and ichthyosiform consistency of the skin which have been described by Urbach and Wiethe[1246] in lipoidproteinosis on the fingers and other peripherally located areas and which are probably caused by the fact that the vessels of the stratum papillare are packed with lipoid which slows up the circulation considerably and hinders the normal metabolic interchange with the overlying epidermis. As we[1247] have pointed out, all this produces a state of chronic irritation which, in turn, gives rise to the formation of hyperkeratoses. The warty lesions which Urbach, Epstein and Lorenz[110] have described in extracellular cholesterosis are probably caused by a similar pathomechanism.

Since in the overwhelming majority of cases xanthelasmas are accompanied by high lipid and cholesterol levels, it was natural to assume that a low fat, and particularly a low cholesterol diet, should be beneficial. In fact, a number of authors, including Jamieson,[1248] Gaal,[1249] Herrmann and Nathan,[1250] Thannhauser,[1251] Edelmann,[828] Stetson and Diasio,[1252] Rowland,[1253] Richter,[1254] and Weber[1255] have observed marked improvement in the cutaneous manifestations and a decrease of the hypercholesterolemia on a diet of this kind.

Thannhauser and Magendantz[1256, 1256a] are of the opinion that a diet low in cholesterol and entirely free of animal fat—that is, a vegetable diet—is of therapeutic value in primary essential xanthomatosis of the hypercholesterolemia type. This view is based on findings reported by Schoenheimer[120] that plant sterols are not absorbed by the human organism. Since it is known that xanthelasma patients have difficulty in excreting cholesterol, a shift from an animal to a vegetable diet serves to stop the influx of cholesterol almost completely and thus to correct the hypercholesterolemia.

In the experience of the present writer, it is practically impossible to keep a patient with disseminated xanthelasma on a diet totally free of animal fat for any length of time and still maintain his ability to work. Such a diet excludes entirely meat of any kind and even skimmed milk and cottage cheese. However, it was found possible to allow well cooked, lean meat once daily if oils of vegetable origin were rigidly excluded from

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1246. Urbach, E. and Wiethe, C.: Arch. f. Dermat. u. Syph. **168:** 94, 1933.
1247. Urbach, E.: Arch. f. Dermat. u. Syph. **174:** 400, 1936.
1248. Jamieson: Arch. Dermat. & Syph. **8:** 877, 1923.
1249. Gaal, A. M.: Ztschr. f. klin. Med. **113:** 349, 1930.
1250. Herrmann, F. and Nathan, E.: Arch. f. Dermat. u. Syph. **152:** 575, 1926.
1251. Thannhauser, S. J.: Klin. Wchnschr. **13:** 161, 1934.
1252. Stetson, D. D. and Diasio, F. A.: Arch. Dermat. & Syph. **18:** 348, 1928.
1253. Rowland, R. S.: Arch. Int. Med. **42:** 611, 1928.
1254. Richter, W.: München. med. Wchnschr. **76:** 2163, 1929.
1255. Weber, P.: Cutaneous Xanthoma and Xanthomatosis of Other Parts of the Body. London: Lewis, 1927.
1256. Thannhauser, S. J.: Schweiz. med. Wchnschr. **65:** 1177, 1936.
1256a. Thannhauser, S. J. and Magendantz, H.: Ann. Int. Med. **11:** 1662, 1938.

the diet. As shown in Table 87 on page 544, the cholesterol level of the blood was decreased in one case of xanthelasma from 644 mg. per cent to 362 mg. per cent and in a second case from 440 mg. per cent to 267 mg. per cent, and at the same time marked clinical improvement was observed.

In addition to a diet low in fat and cholesterol, we found it advisable to administer insulin in every case of this kind. Insulin seems to exert its influence by lowering the fat and cholesterol levels in the tissues and in the blood. Although detailed discussion of the subject is not feasible here, we strongly recommend a trial with insulin, not only in diabetic xanthelasma, but in all the other forms of xanthelasma. In cases of nondiabetic xanthelasma insulin is given in combination with a diet low in fat and cholesterol, but there is no need for restricting the carbohydrate intake. To begin with, 5 to 10 units of insulin are administered daily; if tolerated, the dosage may be increased to 15 units three times daily.

On the other hand, it has been reported that ingestion of animal fat or of cholesterol has no harmful effect on xanthelasma whatever. Thus, Wile et al.[249] noted no sign of exacerbation when a patient with xanthelasma tuberosum was placed on a diet very high in fat. Greenbaum[1257] found no increase in the size of the xanthelasma in a patient who received 1 Gm. of cholesterol three times daily for almost a month. Sperry and Schick[1258] sought an explanation of the fact that a cholesterol-free diet is beneficial in some cases of xanthelasma and ineffective in others. These authors arrived at the conclusion that results can be expected from this diet only in those cases presenting a highly abnormal ratio of combined cholesterol to free cholesterol.

Wile and co-workers[249] achieved disappearance of the nodules and the hyperlipemia in a number of cases by means of a low caloric diet as prescribed for obesity. They explain the favorable influence of this regimen by its tendency to mobilize depot fat. Similarly, in several cases of xanthelasma on a low caloric diet Montgomery and Osterberg[1259] observed diminution in the size and number of the lesions and reduction of the hyperlipemia. Polano[1260] described a patient whose extensive xanthelasma disappeared spontaneously during dietary restrictions necessitated by the acute food shortage in Holland during World War I.

It is also interesting to note the relationship between vitamin A metabolism and xanthelasma. More than a decade ago Thomson[1261] and Bennhold[1262] stressed the close relationship between carotene and cholesterol, claiming that the yellow color of the xanthelasma nodules was due to their abnormally high carotene content. Wiedmann[827] found the vitamin A level in the blood serum of a patient with xanthelasma increased to 150 units per 10 cc. as compared with the normal figure of 1.4. This observation has been confirmed by Marchionini and Patel[363] and Balbi.[1263] Following treatment with a fat-free diet and insulin, this level was materially reduced and the skin disorder disappeared. The explanation, according to Wiedmann, is that when the ability of the liver to transform carotene into vitamin A and to store the latter is impaired, the organism becomes flooded with vitamin A. This, in turn, promotes excessive production of fatty bodies, particularly of phospholipid substances, the accumulation of which leads to the formation of xanthelasma. The therapy outlined by Wiedmann should be given a thorough trial. Reduction of the vitamin A intake calls for exclusion of the following foods from the diet: vegetables (escarole, spinach, carrots, red pepper, tomatoes, peas, lettuce), fruits (apricots, mango, prunes), dairy dishes (butter, cream cheese, eggs, dried whole milk), beef liver, kidneys, and oysters.

[1257] Greenbaum, S. S.: personal communication.

[1258] Sperry, W. M. and Schick, B.: Am. J. Dis. Child. **51:** 1372, 1936.

[1259] Montgomery, H. and Osterberg, A. E.: Arch. Dermat. & Syph. **37:** 373, 1938.

[1260] Polano, M. K.: Arch. f. Dermat. u. Syph. **174:** 213, 1936.

[1261] Thomson, J. G.: Ztschr. f. d. ges. exper. Med. **92:** 692, 1934.

[1262] Bennhold, H.: Klin. Wchnschr. **13:** 36, 1934.

It is rather difficult to reconcile Montgomery's[1264] report with Wiedmann's findings, for the former states that he obtained good clinical results with treatment consisting of vitamin A (200,000 units) plus 0.5 Gm. (7½ grains) of dehydrocholic acid daily for five months. This may have been due to the beneficial effect of the choline on the liver.

The well known lipotropic effect of lecithin and choline induced Adlersberg and Sobotka[123] to administer lecithin in the treatment of five cases of xanthelasma with hypercholesterolemia. They reported a striking decrease in the serum cholesterol and some clinical improvement following prolonged administration of lecithin. However, a few months after the lecithin feeding was stopped, the serum cholesterol returned to its original high level. Similar observations have been reported by Gross and Kesten[124] and Combes.[250] In the present writer's cases the combination of lecithin with an animal and vegetable fat–free diet produced excellent clinical results after four months, as shown in Figs. 254, 255 and Table 26. Curtis and Berger[1264a] employed soy bean lecithin complex in the treatment of xanthelasma without significant effect on the cutaneous lesions or the blood lipids. These authors suggest that it may be necessary to give larger doses of soy bean lecithin than have been employed heretofore. Moreover, we have shown that such therapy must be reinforced by a diet free of animal and vegetable fats (Table 87).

Since diabetic management is the therapy of choice in xanthelasma diabeticorum, a sugar tolerance test should be performed in every case of xanthelasma. The amount of fat included in the diet is said to be of secondary importance, for the reason that the derangement in fat me-

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1263. Balbi, E.: Arch. ital. di dermat., sif. e vener. 14: 537, 1938.
1264. Montgomery, R. M.: Arch. Dermat. & Syph. 51: 214, 1945.
1264a. Curtis, A. C. and Berger, J. C.: Arch. Dermat. & Syph. 51: 214, 1945.

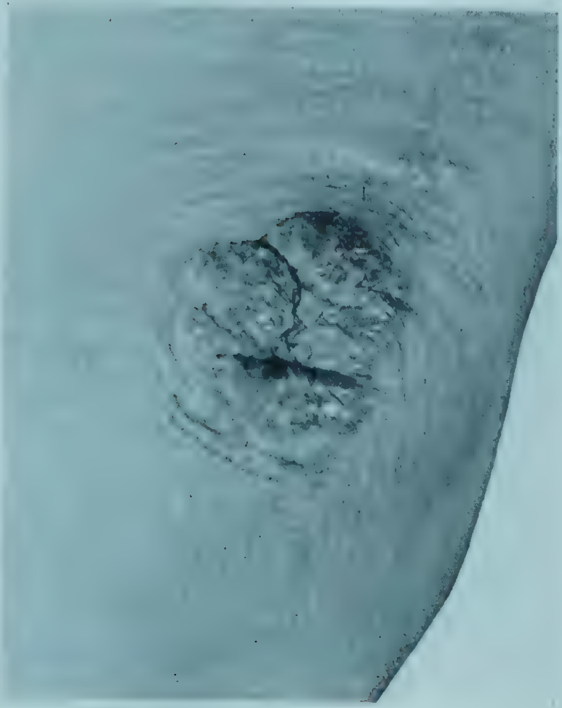

FIG. 254

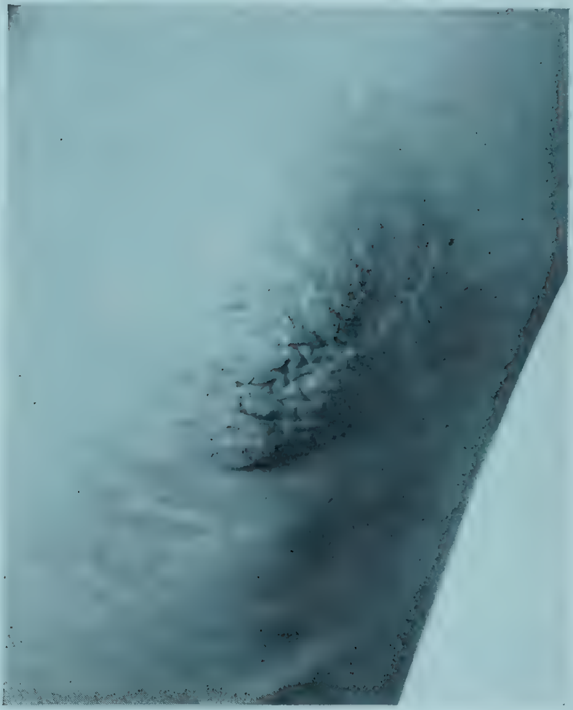

FIG. 255

EFFECT OF FAT-FREE DIET ON XANTHELASMA

FIG. 254. Before therapy.

FIG. 255. After eight months of fat-free diet.

tabolism is a consequence of the diabetic state. Thus, Wile et al.[249] report a number of cases in which the xanthelasma regressed on a diet low in carbohydrate but relatively high in fat. On the other hand, in the same patients the administration of sugar was followed by an increase of the lipemia and of the size of the xanthelasma.

The present writer recently studied the difference of various diets in the management of xanthelasmatosis in two brothers and came to the definite conclusion that a regimen practically free of both animal and vegetable fat, moderate in carbohydrates, and with lecithin added can produce remarkable clinical results accompanied by a decided decrease of the blood cholesterol levels. It may be added that the blood sugar tolerance test was entirely normal in both brothers. Table 87 gives a summary of the trial diets together with their influence on the blood and skin sugar levels and the ratio between them, the total blood cholesterol and cholesterol esters. The figures correspond with experimental findings of Urbach and

TABLE 87.—*Influence of Various Dietaries on the Blood Sugar and Skin Sugar and the Blood Cholesterol in a Case of Xanthelasma*

Diets	Weeks	Blood Sugar	Skin Sugar	Ratio $\frac{\text{Skin}}{\text{Blood Sugar}}$	Total Cholesterol	Cholesterol Esters	Weight	Clinical Remarks
Normal	—	95	57.0	60	520	—	179	Xanthelasma on elbows, palms, fingers, toes
Low carbohydrate	6	97.1	59.8	61.6	644	480	176	No change
Free of animal fat	6	106	65.2	61.5	464	220	170	No change
Free of animal fat, poor in animal protein	6	108	66.9	61.9	560	298	168	No change
Free of animal and vegetable fat	8	106	64.1	60.4	316	186	166	Improvement
Free of animal and vegetable fat, low carbohydrate	5	94	59.5	63.3	378	249	165	Further improvement
Free of animal and vegetable fat, high carbohydrate	4	103.5	65.6	63.4	362	240	168	No change
Free of animal and vegetable fat plus 50 Gm. of soya lecithin	5	94	67	71.3	306	228	171	No change
Free of animal and vegetable fat, 50 Gm. lecithin rich in carbohydrates	6	97	64	66	376	322	174	No change
Free of animal and vegetable fat, low in carbohydrate plus 50 Gm. of lecithin	6	96.6	66.6	68.5	321	228	168	Great improvement

Lentz[248a] which demonstrate that high fat meals lower the blood sugar and skin sugar while a low fat diet causes an increase.

Another important lipoid disease with a diabetic basis is a dermatosis which has been termed "necrobiosis lipoidica diabeticorum" by Urbach[1265] and "dermatitis atrophicans maculosa lipoides diabetica" by Oppenheim[1266] (Figs. 256, 257). Although hyperlipoidemia and hypercholesterolemia almost invariably appear, the present writer suggested that the condition should properly be considered as a localized lipoidosis because the dominant symptom, necrobiosis, is in his opinion the underlying cause of the local deposition of lipoid. The diabetic etiology of this disease was challenged for a short time. However, in a painstaking review of the literature, Hildebrand, Montgomery, and Rynearson[1267] established the fact that the condition was associated with diabetes mellitus in more than 87 per cent of all cases described. While the cutaneous lesions developed several months or years after the onset of diabetes in most instances, the reverse was true in some 18 per cent of the cases encountered in the literature in which the cutaneous lesions preceded the onset of diabetes by as much as eight years. In 10 per cent of patients without demonstrable

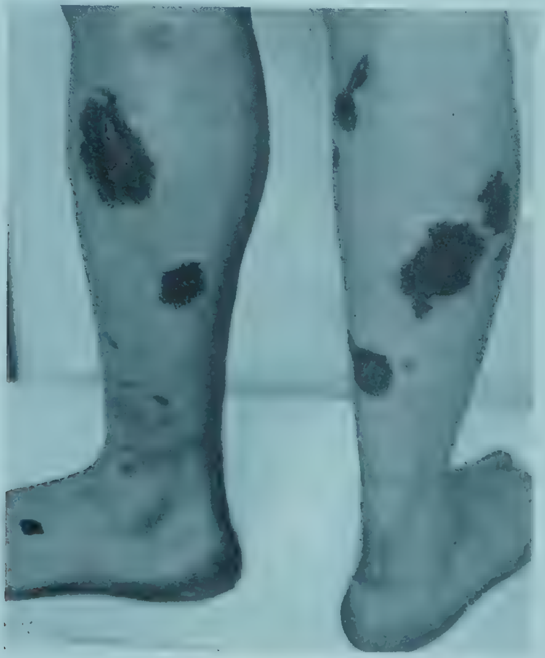

FIG. 256. NECROBIOSIS LIPOIDICA DIABETICORUM

Showing distribution.

1265. URBACH, E.: Arch. f. Dermat. u. Syph. **166:** 273, 1932.

1266. OPPENHEIM, M.: Arch. f. Dermat. u. Syph. **166:** 576, 1932.

1267. HILDEBRAND, A. G., MONTGOMERY, H., and RYNEARSON, E.: Ann. Int. Med. **66:** 851, 1940.

diabetes the majority gave a history of a familial incidence of diabetes or of abnormal sugar tolerance curves. It is therefore possible that the lesions of necrobiosis lipoidica observed in a patient without diabetes merely represent a prodromal stage and that diabetes will ultimately

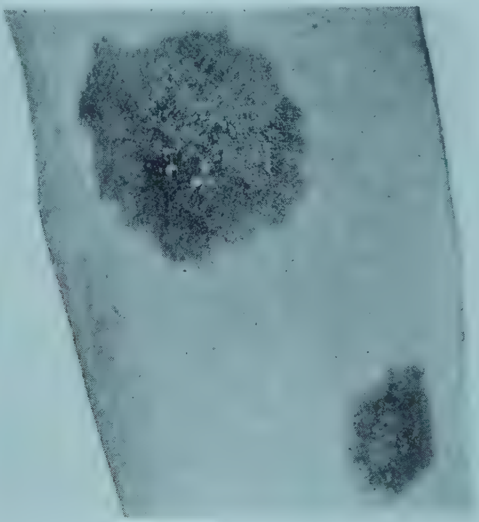

Fig. 257. Necrobiosis Lipoidica Diabeticorum

Close view of lesions.

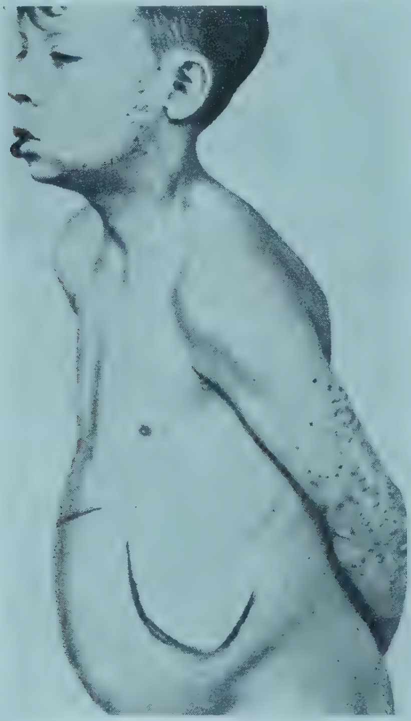

Fig. 258. Hepatosplenomegalic Lipoidosis of Buerger-Gruetz

develop (Ormsby and Montgomery[915]). The present writer recommends that the skin sugar level be determined in every case in which the blood sugar tolerance curve is normal because, in his experience, the former will give far more information concerning any disorder of the sugar metabolism in the skin (see p. 84).

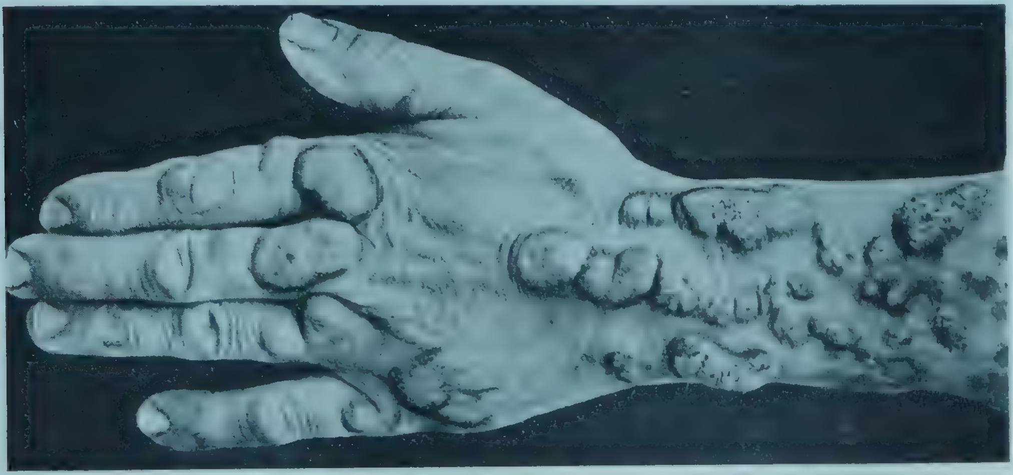

FIG. 259. EXTRACELLULAR CHOLESTERINOSIS

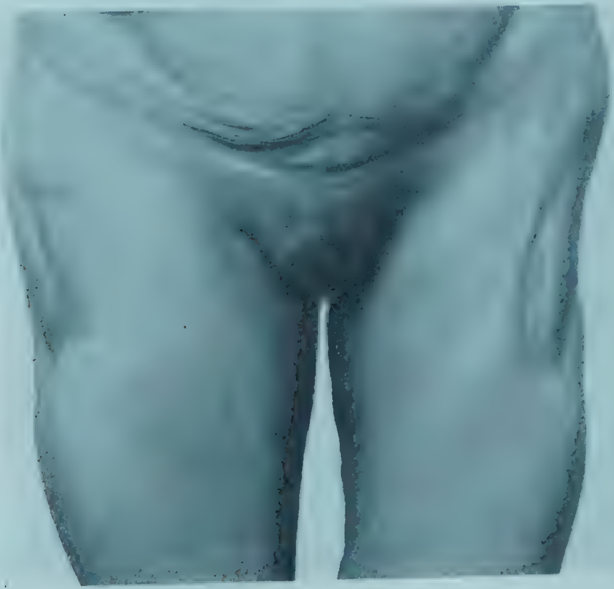

FIG. 260. LOCAL FAT ATROPHY DUE TO INSULIN

Treatment of necrobiosis lipoidica consists primarily of control of the underlying diabetes. The writer recommends a diet very low in fat and moderately high in carbohydrates, supported by insulin. In his patient, after some six weeks of rigid adherence to this diet and regular administration of insulin (10 to 15 units three times daily), the hard plaques began to soften and their color to fade from blue-violet to pale lavender. An attempt was then made to promote further resorption of the locally accumulated lipoid by means of local injections of insulin around and under the individual lesions. We feel that this served to accelerate the mobilization of the lipoids fixed in the necrotic tissue. The cholesterol and sugar levels in the blood returned to normal under this treatment. Gross and Machacek,[1268] Michelson,[1269] and Kren[1270] also observed that this regimen produced marked retrogression of the affected cutaneous areas, although others report that they were unable to achieve any improvement by these procedures. Successful mobilization of fat seems to depend largely on meticulous adherence to a diet practically free of animal and vegetable fat and administration of insulin in adequate amounts. On the basis of recent experiences we would suggest the addition to the diet of soya lecithin, 50 Gm., or Granulestin (Associated Concentrates, Inc.), 35 Gm., daily.

In hepatosplenomegalic lipoidosis of Buerger and Gruetz[829] (Fig. 258), Gruetz[1271] as well as Schrade[1272] kept patients on a low fat diet for several months and noted improvement of the cutaneous and mucous manifestations as well as of the enlarged liver and spleen. At the same time the blood lipoids dropped very nearly to normal levels. When the dietary therapy was suspended all the manifestations reappeared, only to disappear again when the low fat regimen was resumed.

In the case of extracellular cholesterinosis (Fig. 259) which has been described above,[110] we did not employ any dietary therapy. However, the fact that oral administration of 5 Gm. of cholesterol plus 100 Gm. of olive oil caused a visible, if only transitory, enlargement of the tiny, yellow nodules around the conjunctival limbus proves that a diet high in fat is definitely contraindicated.

Lastly, we might mention a form of local fat atrophy due to insulin therapy described by Depisch.[1273] This condition, which is encountered in diabetic individuals and caused by repeated injections of insulin in the same skin site, is characterized by the simultaneous disappearance of fat in the center of the area and its increase in the periphery. It is termed insulin lipodystrophy (Fig. 260).

[1268] Gross, P. and Machacek, G. F.: Arch. Dermat. & Syph. **32:** 491, 1935.

[1269] Michelson, H. E.: Arch. Dermat. & Syph. **33:** 900, 1936.

[1270] Kren, O.: Zentralbl. f. Haut- u. Geschlechtskr. **49:** 580, 1935.

[1271] Gruetz, O.: Zentralbl. f. Haut- u. Geschlechtskr. **49:** 296, 1935.

[1272] Schrade, W.: Verhandl. d. Ges. f. Verdauungs- u. Stoffwechselkr xiii tagung, 1936, p. 211.

[1273] Depisch, F.: Klin. Wchnschr. **16:** 605, 1937.

CHAPTER XXI

Wounds, Ulcers, Burns

IT has long been known that the diet has an effect on wound healing. Thus, the fact that wounds heal poorly in scurvy was recognized nearly two hundred years ago. While the frank stage of this disease is rare, preclinical or symptomatic scurvy is not uncommon in this country. We are indebted to Crandon, Lund, and Hill[493] for the first controlled experiments. By self-experimentation, Crandon demonstrated that adherence to a diet deficient in ascorbic acid for three months resulted in no interference with normal wound healing but that after six months a similar wound failed to heal properly. Hunt[1274] has shown that the factors essential to the healing of wounds, such as migration and proliferation of epidermal and mesodermal cells, the production of an intercellular matrix, and the formation of new blood vessels, are dependent on an adequate supply of ascorbic acid in the tissues.

A low protein intake constitutes another important dietary factor tending to delay the healing of wounds. The healing of wounds, ulcers, and burns, depending as it does on cell regeneration, requires protein-building elements. The need for a high protein diet to promote prompt healing, and the frequent association of protein deficiencies with delayed reparative processes, have repeatedly been pointed out (Clark,[1275] Koster and Kasman,[1276] and others). More recently, Thompson, Ravdin, and Frank[1277] made a study of the effect of hypoproteinemia on tissue repair and found that a reduction of 15 per cent in plasma protein may lead to a moderate delay, while a reduction of 25 per cent is severe enough to cause very considerable delay or complete failure of healing. For these reasons, patients with cutaneous or surgical wounds should receive a diet high in protein and vitamins.

Unsatisfactory healing is not always due to an inadequate intake of protein or of certain vitamins. The delay is very commonly caused by some infection. Hippocrates recognized the fact that fasting, catharsis, and restriction of the liquid intake constitute important measures in the management of infected wounds. Sauerbruch[160] and Herrmannsdorfer[1278] noted improvement on the diet (p. 70) which bears their names, and expressed the opinion that these good results should be attributed to the

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1274. Hunt, A. H.: Brit. J. Surg. **28:** 436, 1941.
1275. Clark, A. H.: Bull. Johns Hopkins Hosp. **30:** 117, 1919.
1276. Koster, H. and Kasman, L. P.: Arch. Surg. **45:** 776, 1942.
1277. Thompson, W. D., Ravdin, I. S. and Frank, I. L.: Arch. Surg. **36:** 500, 1938.
1278. Herrmannsdorfer, A.: Arch. klin. Chir. **138:** 396, 1925.

tendency of the diet to acidify the tissues. Von Noorden,[172] however, regards the very low dietary content of sodium chloride as the decisive factor here, since he obtained similarly good results with a diet limited to fruit, which is extremely poor in salt. Furthermore, he recommended his zigzag diet (p. 125) together with a sharp restriction of the sodium chloride intake.

Generally speaking, conditions in cutaneous ulcers are similar to those in wounds. This is readily understandable; for, although they are produced by a variety of causes (impaired circulation, infection, pressure), once developed, ulcers always represent a loss of tissue on the part of the skin due to destruction of cutaneous connective tissue. The fact has been mentioned above that both protein and vitamin C are essential to the proliferation of fibroblasts. In this connection it is particularly interesting to note reports by Mulholland,[299] Altschuler,[298] and their associates that nonhealing ulcers of varicose, diabetic, and decubital origin may respond with striking improvement to treatment with protein hydrolysates (see p. 119). In addition, these authors recommend ascorbic acid and an abundant, well balanced diet. By these dietary measures they achieved healing within three to six weeks in cases which had remained stationary for a year or longer. Vorhaus et al.[471] stress the efficacy of riboflavin and other members of the vitamin B complex, notably in decubital ulcers.

Even in tropical ulcers, which are caused by various infections, the importance of a well balanced diet rich in protein and vitamins in maintaining resistance to this disease was stressed by Clements,[1279] Charters,[1280] and others. According to Livingood,[1281] Dermatological Consultant to the Surgeon General of the Army, the American soldier in World War II was rarely affected by tropical ulcer, probably because he was well fed, while the natives frequently developed this condition because of their poor diet.

In cases of diabetic ulcer it is advisable to give the indicated dietary therapy supported by insulin plus intravenous administration of vitamin B complex. The present writer[1282] has had occasion to observe an interesting case of phagedenic ulcer due to skin diabetes (hyperglycodermia without hyperglycemia). The condition did not yield until the patient had been placed on a diabetic diet, supported by insulin therapy (Fig. 261).

Ulcera cruris occasionally respond rather well to the Sauerbruch-Herrmansdorfer diet (Axmann,[1229] Volk[1169]). The present writer has also seen a case of deep-seated ulcer due to thrombophlebitis which yielded only when the patient was placed on this regimen (Fig. 262).

1279. Clements, F. W.: J. A. M. A. 117: 114, 1941.
1280. Charters, A. D.: Tr. Roy. Soc. Trop. Med. & Hygiene 37: 205, 1943.
1281. Livingood, C. S.: Philadelphia Medicine 41: 156, 1945.
1282. Urbach, E.: Klin. Wchnschr. 16: 1315, 1937.

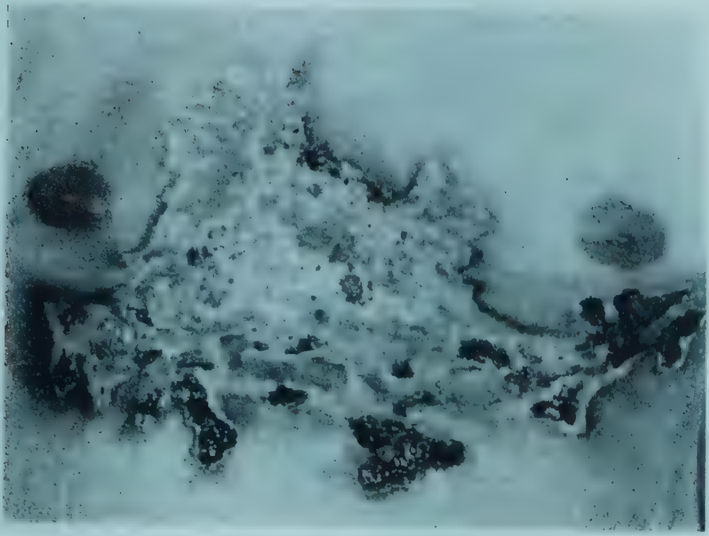

Fig. 261. Phagedenic Ulcer Associated with Skin Diabetes

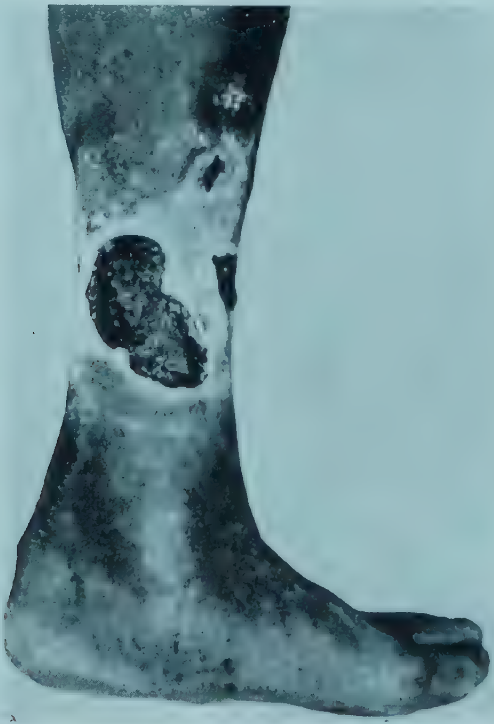

Fig. 262. Ulcus Cruris Due to Thrombophlebitis

Healing after prolonged use of Sauerbruch-Herrmannsdorfer diet.

Bommer[195] obtained satisfactory results with the Sauerbruch-Herrmannsdorfer diet in cases of roentgen damage to the skin. There is a definite reduction of the characteristic inelastic doughy consistency of the skin during the first few weeks; the skin becomes smoother and regains its lost pliability as it is loosened from the underlying tissues to which it has been attached so firmly that it could not be moved or pinched, and the telangiectases gradually decrease in size and number. Hyperkeratoses and warty growths may vanish. Microscopic examination of the capillaries also reveals a return to normal size, and reduction of the edema; moreover, normal development of fine terminal loops can be seen.

These findings have been confirmed by Volk,[202] who added that even severe, highly refractory roentgen ulcers may respond in this manner. Volk goes so far as to speak of a cure of this notoriously intractable form of roentgen injury. The present writer observed a case of extensive ulceration due to irradiation in whom, despite three months of continuous bath treatment, the condition became steadily worse. However, when the patient was placed on a Sauerbruch-Herrmannsdorfer diet and kept in the continuous bath a virtually complete cure was achieved within nine weeks.

Kalk[167] observed a roentgen ulcer of more than twenty years' duration; when a carcinoma of the esophagus interfered with the patient's eating to such an extent that he was literally starving, the roentgen ulcer spontaneously disappeared. Similar observations have been reported by Graninger.[1283]

In this connection we should like to mention the excellent results obtained by Bommer[195] in hypertrophic scars with the low salt diet. Under this dietary therapy, the raised scar tissue receded to the level of the surrounding skin, became paler and less noticeable. According to Gerson,[198] even keloids will retrogress appreciably under this treatment; after a few months they become softer, flatter, and lose their abnormal coloration. These findings have been confirmed by Volk.[202]

Investigations carried out during the past few years have disclosed that nutritional or, more explicitly, protein therapy is of the utmost importance in the treatment of thermal burns. Extensive burns invariably lead to a state of acute hypoproteinemia, of which there are two different types: the early and the late. The early type occurs in the shock phase, is quite rare, and is often due to overtreatment with crystalloid solutions given parenterally, or to loss of plasma. The late type commonly occurs in the granulating phase and is due to metabolic protein imbalance, increased excretion of nitrogen in the urine (as high as 28 to 45 Gm. a day), great loss of protein from the granulating surfaces, and destruction of protein by coincidental infection (Harkins[1284]). When the burns are extensive, there is often a huge loss of plasma proteins through transudation of fluid from the burned areas. Thus, Hirschfeld and his associates[1285] demonstrated that the surface loss of protein might amount to 25 per cent of the total nitrogen loss. In absolute terms, one of their patients lost some 8 Gm. of nitrogen a day from the surface of the burn.

[1283] Graninger, K.: Strahlentherapie **38:** 775, 1930.

[1284] Harkins, H. N.: Arch. Path. **38:** 147, 1944.

There can be no doubt that many deaths following burns which were formerly attributed to infection were due primarily to the development of such severe hypoproteinemia and poor nutritional state that the patient was stripped of his resistive powers (Lee et al.[1286]). This view is supported by the recent studies of Cannon and his associates[1287] on the relationship between protein metabolism and resistance to infection.

To prevent a protein deficit, as evidenced by progressive hypoproteinemia, poor granulation tissue, and pronounced loss of weight, a very substantial protein intake is required. Moreover, the great fluid loss from the denuded skin surfaces leads to dehydration, accompanied by a decrease in the circulating plasma volume and consequent hemoconcentration as evidenced by the increase in the number of red cells in the whole blood. Therefore, in addition to local measures, such as penicillin, sulfonamides, and adequate supporting bandages, treatment should include such systemic measures as plasma infusions as well as oral and intravenous administration of fluids and proteins. An excellent summary of the treatment of burns was recently presented in a memorandum prepared by a special committee (Harkins, Cope, Evans, Phillips, and Richards, Jr.[1288]), and we can do no better than quote from this paper. "Treatment should consist of: (A) Oral Therapy: a full food intake, including calories, vitamins, and, most particularly, protein.

"1. Total fluid should be sufficient to keep the urine volume 1,500 cc. or higher daily. If salt intake has been adequate, body proteins not too much depleted and heart and kidney function competent, this usually means an intake of between 3,000 and 4,000 cc. daily.

"2. Salt (sodium chloride) intake should be maintained around 10 Gm. daily; a little higher if the burn is extensive, with much exudate. Too much salt, however, promotes general tissue edema. Blood carbon dioxide tends to run somewhat low, and some alkaline salt is advisable. Try to keep the urine about neutral to litmus. The physiologic electrolyte solution 1,000 to 1,500 cc. daily will often be useful during the first five to ten days. Water can be given *ad libitum* after the fourth day.

"3. Diet should be high in protein, carbohydrate, calories, and vitamins. The protein intake should be added to with increasing areas of third degree

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1285. Hirshfeld, J. W., Williams, H. H., Abbott, W. E., Heller, C. G. and Pilling, M. A.: Surgery **15:** 766, 1944.

1286. Lee, H. E., Walker, J. Jr., Pressly, L. and Rhoads, J. E.: Pennsylvania M. J. **48:** 563, 1945.

1287. Cannon, P. R., Wissler, R. W., Woolridge, R. L., and Beuditt, E. P.: Ann. Surg. **120:** 514, 1944.

1288. Harkins, J. W., Cope, O., Evans, E. I., Phillips, R. A. and Richards, D. W. Jr.: J. A. M. A. **128:** 475, 1945.

burns as early as possible after the injury and probably by the end of the first week. Such protein intake should be of the following magnitudes: 5 to 10 per cent body surface burned, 125 Gm. of protein per day; 10 to 20 per cent of body surface burned, 125 to 200 Gm. of protein per day; more than 20 per cent of body surface burned, more than 200 to 300 Gm. of protein per day, provided the patient's gastrointestinal tract can tolerate these large amounts. The corresponding caloric intake should be approximately 3,000, 4,000, or 5,000 calories per day.

"(a) Amino acids by mouth, 100 to 200 Gm. per day, are an effective form of protein intake but difficult to tolerate because of the bad taste. Few patients can take them for more than three or four days.

"(b) An example of an adequate diet is that used by Evans, which is palatable by mouth but also can be given by tube, as follows: 150 Gm. of dehydrated meat powder, 150 Gm. of powdered whole milk, 50 Gm. of corn oil, 150 Gm. of sucrose, 150 Gm. of Dextrimaltose, 35 Gm. of chocolate, and 1,000 cc. of water (plus vitamins, especially A, B, C, and D, and iron).

"(c) Adequate vitamins and iron are essential in all unhealed burns. A suggested daily dosage is as follows for burns of 20 per cent area of third degree. Correspondingly smaller doses should be used for less severe burns: vitamin A, 20,000 units; vitamin B: thiamine hydrochloride, 40 mg.; riboflavin, 20 mg.; niacin amide, 50 mg.; vitamin C, 1 Gm.; vitamin D, 2,000 units; vitamin K, 1 mg.; ferrous sulfate, 1.5 Gm.

"B. Intravenous Therapy.—1. Plasma or albumin is seldom necessary after the second day. A 500 cc. plasma transfusion usually contains less than 30 Gm. of plasma protein; a severely burned patient needs 150 to 200 Gm. of protein a day. Hence, while plasma transfusions are helpful in combating hypoproteinemia, they are quantitatively insufficient to accomplish much in this regard.

"2. Amino acid solutions, as now available, can usually be tolerated intravenously in amounts up to 100 to 150 Gm. of amino acids in a 10 per cent solution if administered slowly. They are helpful during the first week or longer (after shock has been relieved) in sustaining and restoring the patient's state of nutrition but are indicated only if the patient cannot take adequate proteins by mouth."

If necessary, adequate feeding can be accomplished by administering protein hydrolysates through an indwelling duodenal or jejunal tube (Beling and Lee).

CHAPTER XXII

Pigmentary Diseases of the Skin

Of the numerous skin pigmentations which were recently so brilliantly reviewed by Jeghers[505] and Becker[1290] we shall discuss here only those conditions which are caused or influenced by nutrition or by diseases of the gastrointestinal tract.

Carotenoderma, a yellowish discoloration of the skin, was discussed at some length on page 132. This condition is caused by pathologic amounts of carotene in the blood (carotenemia) due to ingestion of excessive quantities of foods containing carotene, especially carrots, oranges, egg yolk, pumpkin, and squash, and to a lesser extent to an overabundance of green vegetables in the diet. However, as Edwards and Duntley[1291] have demonstrated, carotene is physiologically present in the skin, imparting a yellow component to the normal color of the skin. It is interesting to note that female subjects show considerably more carotene throughout the skin than do males. Carotene is normally present in the stratum corneum in amounts proportional to the thickness of this epidermal layer, and also in the dermal and subcutaneous fat; the sebaceous material contains a small quantity of carotene.

Mu,[381] Pillat,[1292, 1293] and their co-workers found that pigmentation of the skin and conjunctivas, due to severe vitamin A deficiency, was not uncommon among Chinese and Indian patients. In these cases the skin showed varying degrees of generalized discoloration, ranging from brownish to a dull slaty hue, as well as pigmentation of the hyperkeratotic papular lesions. That the cause of the cutaneous and conjunctival pigmentation might well be vitamin A deficiency was suggested by the high incidence of such pigmentation among persons suffering from xerosis, keratomalacia, and follicular hyperkeratosis as well as by the fact that the discoloration gradually faded when the other lesions healed in response to administration of cod liver oil. In the white race, melanin pigmentation due to vitamin A deficiency seems to be a rarity, possibly because, as Jeghers[505] pointed out, a deficiency sufficiently severe and prolonged to cause xerosis and keratomalacia occurs only in exceptional instances. However, a pertinent case has been described by Tolmach and Graham.[379]

Recent investigations by Hathaway[1294] seem to indicate some relationship between vitamin B deficiency and vitiligo. He reported that seven

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1290. Becker, S. W.: Clinics **3:** 886, 1944.
1291. Edwards, E. A. and Duntley, S. Q.: Am. J. Anat. **65:** 1, 1939.
1292. Pillat, A. and King, G.: Brit. J. Ophth. **13:** 506, 1929.
1293. Pillat, A.: Arch. Ophth. **9:** 25, 1933.
1294. Hathaway, J. C.: Arch. Dermat. & Syph. **52:** 117, 1945.

of fourteen patients with this condition showed complete clearance, and two great improvement of the depigmentation from taking two vitamin B complex capsules fortified with niacin, thiamine hydrochloride, and riboflavin plus hydrochloric acid. This therapy has to be continued for one or two years. Injection of these vitamins may give quicker results.

The relationship between pigmentation and vitamin C was briefly mentioned on page 192. Here we should like to call attention to the pathologic cutaneous pigmentation seen in scurvy, gastric carcinoma, sprue, chronic gastrointestinal and pancreatic disturbances, and pernicious anemia in which an insufficiency of vitamin C in the diet or inadequate absorption of this vitamin by the intestine is believed to cause the pigmentary disturbance. The beneficial effects of ascorbic acid administered either orally or parenterally, depending on the cause of the vitamin C deficiency, have been described by Hoff,[501] Cornbleet,[499] and Schroeder and Einhauser.[498] Moreover, abnormal cutaneous pigmentation may also be attributable to a lack of endogenously produced ascorbic acid due to destruction of the suprarenal glands, as in Addison's disease. Thus, Cornbleet,[499] Rothman,[504] Abt and Farmer,[500] and others have observed some decrease in pigmentation in Addison's disease following administration of massive doses of ascorbic acid. Others (Morawitz,[1295] Riehl, Jr.,[502] Hruszek[503]) saw facial chloasma disappear in response to similar therapy. Further evidence of the influence of vitamin C on pigment metabolism is furnished by findings, reported by Urbach and Kral,[508] that ascorbic acid taken internally in combination with external applications of natural oil of bergamot affords protection against ultraviolet rays, thus preventing pigmentation (Figs. 263, 264).

While all the cutaneous pigmentations mentioned in the preceding paragraphs are conditions due to vitamin deficiencies, Feer,[340] Jadassohn and Schaaf,[341] and Rodecourt[342] have described generalized pigmentation occurring only in children with dark skins who have received large quantities of vitamin D. It is believed, however, that this is fundamentally due to a relative deficiency of vitamin C resulting from disturbance in the physiologic relationship between the two vitamins when vitamin D is given in excessive quantities.

There seem to be several varieties of pigmentary abnormalities associated with pellagra. The most common type is the deep tan discoloration which develops on the exposed parts of the body, such as the face, neck, back of the hands, and lower legs (Smith and Ruffin[1296]) and occasionally also in areas subjected to mechanical irritation, such as the elbows and knees (Ruffin[1297]) (Fig. 203, p. 467). Lastly, some of the cases present a brownish pigmentation over the entire body, resembling the discoloration

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[1295] Morawitz, P.: Klin. Wchnschr. **13:** 324, 1934.

[1296] Smith, D. T. and Ruffin, J. M.: Arch. Int. Med. **59:** 631, 1937.

[1297] Ruffin, J. M.: M. Clin. North America **27:** 485, 1943.

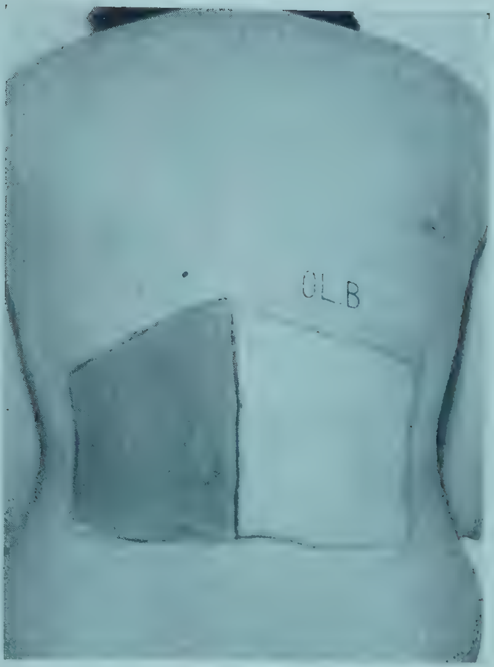

FIG. 263

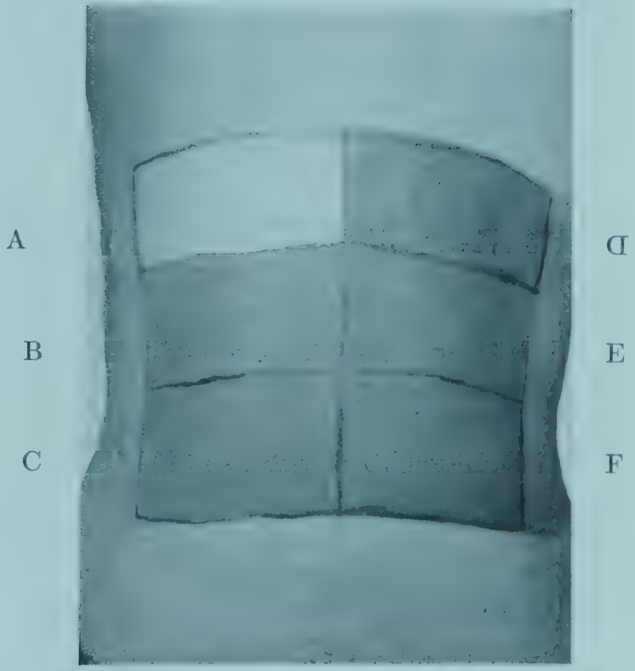

FIG. 264

LIGHT PROTECTION BY COMBINED ACTION OF ASCORBIC ACID AND OIL OF BERGAMOT

FIG. 263. Basic experiment: The patient received 500 mg. of ascorbic acid intravenously. One hour later the area on the right was rubbed with oil of bergamot while the area on the left served as a control. Then both areas were simultaneously given an erythema dose of ultraviolet light. Note that the area treated with oil of bergamot is fully protected.

FIG. 264. A. Treated with oil of bergamot. B. Treated with oil of lemon. C. Treated with oil of caraway. D, E, F. Controls receiving no treatment.

All areas had been exposed to an erythema dose of ultraviolet light one hour after intravenous injection of 500 mg. of ascorbic acid.

Note protective action only of oil of bergamot.

seen in Addison's disease and possibly due to impaired adrenal function (Harris and Harris[1298]).

Pottenger[242] described a peculiar bronze cast following exposure to sunlight which he interpreted as an expression of a disturbance in the fat metabolism arising from ingestion of purified vegetable or meat fat that had been subjected to very high heat. This discoloration responds to treatment with soy bean lecithin.

Riehl's[1175] war melanosis and its possible nutritional etiology were discussed on page 515.

Recent experimental findings suggest that copper may serve as a catalyst in the formation of pigment in the skin and hair of mammals. Thus, Keil and Nelson[101] report that when rats are fed nothing but milk (i.e., a diet extremely low in copper) their fur undergoes marked pigmentary changes, the black hairs turning silvery gray. The normal color of the fur is promptly restored, however, when the animals are fed small amounts of copper. Similarly, Gorter[1299] achieved striking depigmentation of animal fur by dietary means, and cured this condition by administering copper. By actual analysis Cunningham[1300] demonstrated that the copper content of the skin of black rats and rabbits generally exceeds that of otherwise comparable white animals. Sarato[1301] found that the black and brown hair of dogs and cats contained 50 per cent more copper than did the white hair. Recalling the recognized fact that, in a certain dilution, the copper ion is capable of accelerating the spontaneous oxidation of a 3,4 dioxyphenylalanin solution, Sarato feels justified in the conclusion that copper plays the role of a catalyst in the process of pigment formation. Cornbleet[499] has suggested that a disturbance in the balance of the copper–vitamin C–melanin mechanism of the skin is the explanation of the cutaneous pigmentation in Addison's disease and scurvy. The importance of keeping this pigmentogenous property of copper in mind is illustrated by a case reported by Alt[1302] in which darkly pigmented moles appeared on the skin following copper therapy for anemia. Alt believes that copper was instrumental in the production of the pigmentation in this patient.

The influence of diets deficient in pantothenic acid or paraminobenzoic acid, especially with regard to changing the color of the hair, was briefly mentioned on page 184. Ansbacher[1303] has presented a thorough discussion of the interesting problem of achromotrichia.

1298. Harris, S. and Harris, S. Jr.: Clinical Pellagra. St. Louis: Mosby, 1941.
1299. Gorter, F. J.: Nature **136:** 185, 1935.
1300. Cunningham, I. J.: Biochem. J. **25:** 1267, 1931.
1301. Sarato, U.: Jap. J. Med. Sci., Trans. ii, Biochem. **3:** 79, 1935.
1302. Alt, H. L.: J. A. M. A. **106:** 1220, 1936.
1303. Ansbacher, S.: Vitamins and Hormones **2:** 217 and 223, 1944.

CHAPTER XXIII

Diseases of the Nails

THE nails are subject to diseases affecting the epidermis and also, although less commonly, to the affections of the corium. Since diseases of the nails are rarely painful and are generally noted only by people interested in them from the point of view of appearances, the literature on the relationship between the nails and nutrition in man is rather meager. However, animal breeders and veterinarians are well aware of the influence of the diet on the hoofs and other horny structures in animals, such as changes in the hoofs following unsuitable diet, metabolic disturbances due to overfeeding and to spoiled fodder (Heller[1304]).

Nutritional disturbances may lead to softening of the nails, known as onychomalacia. The nail bends readily, tends to break or split at the free edge, and often presents one or more longitudinal fissures. In cases of this kind, the present writer prescribes a well balanced diet, including an abundance of milk (1 quart daily) plus calcium gluconate (1 tablespoon three times a day) and viosterol (5,000 units twice daily) and strict adherence to a vegetable diet for several months.

The present writer[315] has described nail dystrophy (Fig. 265) following a long period of undernourishment which a Polish girl suffered during World War I. J. Jadassohn[220] regards a physician's observations on himself of the appearance of transverse furrows on all the fingernails following strict adherence to a vegetable diet for several months as conclusive evidence of the influence of the diet on the nail matrix. In a patient reported by Heller[1305] Beau's lines made their appearance on the nails following severe gastrointestinal disturbances and hepatic disorder. The present writer[1306] saw a case in which white cross-striae (Fig. 266) made their appearance on the nails fifty-five days after coronary occlusion and interpreted these changes as an expression of a severe, generalized, nutritive disturbance resulting from circulatory inadequacy due to myocardial damage.

Broekema[1064] described two cases of koilonychia in patients suffering from achylic hypochloremia. Cure of the chlorosis was followed by marked improvement in the nail disease. As demonstrated by Andreson,[964] koilonychia constitutes a part of the Plummer-Vinson syndrome (see p. 476).

[1304] Heller, J.: Handbuch der Haut- u. Geschlechtskr. ed. by J. Jadassohn. **14:** 1, 1930.

[1305] Heller, J.: Handbuch der Haut- u. Geschlechtskr. ed. by J. Jadassohn. **13:** 2, 1927.

[1306] Urbach, E.: Arch. Dermat. & Syph. **52:** 106, 1945.

In avitaminosis the nails suffer along with the other epidermal structures. White,[384] Reiss,[369] Pillat,[378] Sulzberger,[1041] Urbach, and others have seen dullness, dryness, and brittleness of the nails, together with punctate, pitting, transverse furrows (Beau's lines) and longitudinal ridges, associated with vitamin A deficiency. It is interesting to note, however, that excessive doses of vitamin A may be harmful to the nails, causing them to become thin and brittle, lose their homogenous structure, and acquire conspicuous transverse indentations (Schwemmler[336]).

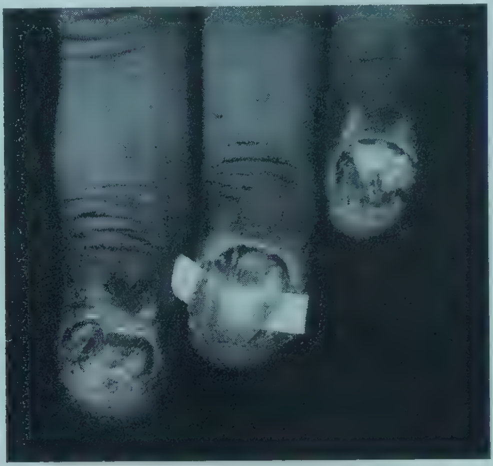

FIG. 265. DYSTROPHY OF NAIL FOLLOWING CHRONIC UNDERNOURISHMENT

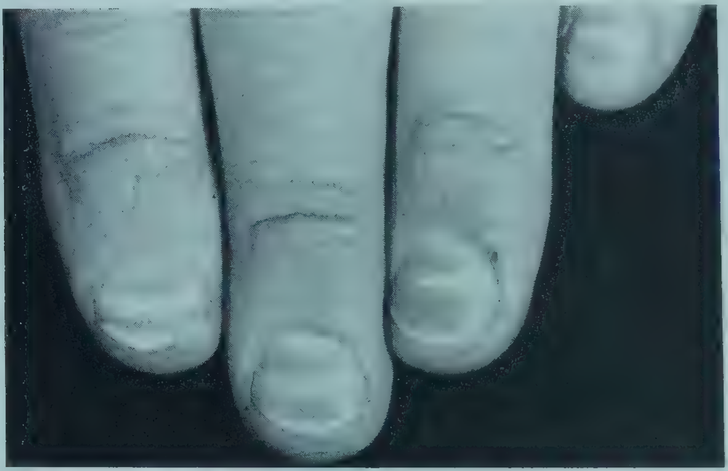

FIG. 266. WHITE CROSS STRIAE OF NAILS

Appeared fifty-five days after acute myocardial infarction, indicating severe generalized nutritive disturbance due to marked circulatory inadequacy.

White[1307] has observed seven cases of nail deformities which he is in-

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1307. WHITE, C.: J. A. M. A. **102**: 2178, 1934.

clined to attribute to chronic hypovitaminosis. They ranged from irregular longitudinal ridging, with slight transverse depressions, to marked dystrophy. Avitaminosis, specifically deficiency in riboflavin and vitamin D due to dietary restrictions, was assumed to be the underlying cause. The introduction of foods and preparations containing these vitamins into the diet was followed by marked improvement in every case.

Scurvy is occasionally associated with subungual bleeding, that is to say, hemorrhages occurring under the nails and appearing as dark blue spots under otherwise unchanged nails.

We feel that chronic paronychia (periungual inflammation about the nail plate) might well be included here. The possibility of diabetes should always be considered first in the presence of this condition; therefore, in addition to performing a glucose tolerance test, it is advisable to try a diabetic diet and even insulin. Paronychia is also not uncommonly an expression of a general state of undernourishment which undermines the organism's powers of resistance and permits infections to gain a foothold. Lastly, this condition is sometimes due to multiple avitaminosis, in which circumstance the paronychia will disappear when the patient is given a suitable diet and the indicated vitamins.

PART FIVE
NUTRITIONAL TABLES

Dietary management requires a knowledge of certain basic factors in addition to data concerning the chemical and biologic composition of the food. It is obvious that the nutritional requirements of an individual depend on his age, sex, weight, height, and activity. For this reason comprehensive tables are presented which give this information for different periods of life.

In keeping with the recommendation of the Council on Pharmacy and Chemistry of the American Medical Association,[1308] we have generally used the metric system to express weights and measures and we have included conversion tables. However, for practical reasons we have often parenthetically included the apothecaries' system equivalent. Moreover, it has been considered expedient to include a list of household weight and capacity measures ordinarily available to any housewife.

The most important information provided in this section is, of course, concerned with the chemical composition of the most commonly used foods with regard to their protein, carbohydrate, fat, mineral, and vitamin content. These food charts are based on a number of authoritative sources, particularly Bridges,[169] McLester,[769] Sherman,[1309] Booher, Hortzler, and Hewston,[1310] Hewston and Marsh,[1311] and the Committee on Food Composition, National Research Council.[1312] However, we have incorporated here only such information as has a direct bearing on the subjects discussed in the body of the book. A table of the recommended daily allowances will be found on page 148.

Since diabetes mellitus plays such a prominent role in the pathogenesis, and therefore the treatment, of dermatoses, a table grouping the fruits and vegetables according to their carbohydrate content is included.

Food allergies constitute another important dietary problem in the management of dermatoses. Elimination regimens are often of great help, and Rowe's[643] basic diets are therefore given in some detail.

Finally, a short list of practical do's and don'ts concludes the section devoted to nutritional tables.

1308. The Metric System: Report of the Council on Pharmacy and Chemistry, J. A. M. A. **123:** 900, 1943.

1309. Sherman, H. C.: Chemistry of Food and Nutrition. New York: Macmillan, 1933.

1310. Booher, L. E., Hortzler, E. R., and Hewston, E. M.: Vitamin Values of Foods. Circular No. 638. U. S. Dep't. Agriculture, 1942.

1311. Hewston, E. M. and Marsh, R. L.: U. S. Dep't. Agriculture, Miscellaneous Publication No. 505.

1312. Tables of Food Composition: Committee on Food Composition of Food and Nutrition Board, National Research Council, 1944.

TABLE 88.—*Age-Height-Weight Table for Adults*

Men

Height	Age									
	19	20	21–22	23–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59
5 ft.	111	112	114	118	122	126	128	131	133	134	135
5 ft. 1 in.	116	117	118	121	124	128	130	133	135	136	137
5 ft. 2 in.	122	123	124	125	126	130	132	135	137	138	139
5 ft. 3 in.	127	128	128	129	131	133	135	138	140	141	142
5 ft. 4 in.	130	131	132	134	135	136	138	141	143	144	145
5 ft. 5 in.	134	135	136	137	138	140	142	145	147	148	149
5 ft. 6 in.	139	140	141	142	143	144	146	149	151	152	153
5 ft. 7 in.	142	143	144	145	146	148	150	153	155	156	158
5 ft. 8 in.	147	148	149	150	151	152	155	158	160	161	163
5 ft. 9 in.	152	153	154	155	156	158	160	163	165	166	168
5 ft. 10 in.	155	156	157	158	159	162	165	168	170	171	173
5 ft. 11 in.	159	160	161	162	164	166	170	174	176	177	178
6 ft.	163	164	165	166	168	172	176	180	182	183	184
6 ft. 1 in.	167	168	169	171	173	178	182	186	188	190	191
6 ft. 2 in.	171	172	174	176	179	184	189	193	195	197	198
6 ft. 3 in.	175	175	178	181	184	190	195	200	202	204	205
6 ft. 4 in.	178	180	183	186	189	196	201	206	209	211	212
6 ft. 5 in.	183	185	188	191	194	201	207	212	215	217	219

The above table, published by the Bureau of Publications, Teachers College, Columbia University, was prepared by Thomas D. Wood, M.D.

TABLE 89.—*Age-Height-Weight Table for Adults*

Women

Height	Age									
	19	20	21–22	23–24	25–29	30–34	35–39	40–44	45–49	50–54
4 ft. 10 in.	104	106	108	110	113	116	119	123	126	129
4 ft. 11 in.	106	107	109	112	115	118	121	125	128	131
5 ft.	112	112	113	115	117	120	123	127	130	133
5 ft. 1 in.	116	116	116	118	119	122	125	129	132	135
5 ft. 2 in.	118	118	119	120	121	124	127	132	135	138
5 ft. 3 in.	120	121	122	123	124	127	130	135	138	141
5 ft. 4 in.	123	124	125	126	128	131	134	138	141	144
5 ft. 5 in.	126	127	128	129	131	134	138	142	145	148
5 ft. 6 in.	130	131	132	133	135	138	142	146	149	152
5 ft. 7 in.	135	135	135	137	139	142	146	150	153	156
5 ft. 8 in.	138	138	139	141	143	146	150	154	157	161
5 ft. 9 in.	142	142	142	145	147	150	154	158	161	165
5 ft. 10 in.	144	144	145	148	151	154	157	161	164	169
5 ft. 11 in.	146	147	149	151	154	157	160	164	168	173
6 ft.	150	152	154	156	158	161	163	167	171	176

The above table, published by the Bureau of Publications, Teachers College, Columbia University, was prepared by Thomas D. Wood, M.D.

TABLE 90.—*Height and Weight Tables for Boys*

4 to 18 Years

Average weights in pounds at successive heights (left column) and ages (top row)

Hgt. (In.)	5 yrs.	6 yrs.	7 yrs.	8 yrs.	9 yrs.	10 yrs.	11 yrs.	12 yrs.	13 yrs.	14 yrs.	15 yrs.	16 yrs.	17 yrs.	18 yrs.
38	34	34												
39	35	35												
40	36	36												
41	38	38	38											
42	39	39	39	39										
43	41	41	41	41										
44	44	44	44	44										
45	46	46	46	46	46									
46	47	48	48	48	48									
47	49	50	50	50	50	50								
48	..	52	53	53	53	53								
49	..	55	55	55	55	55	55							
50	..	57	58	58	58	58	58							
51	..	..	61	61	61	61	61	61						
52	..	..	63	64	64	64	64	64	64					
53	..	..	66	67	67	67	67	68	68					
54	..	..	..	70	70	70	70	71	71	72				
55	..	..	..	72	72	73	73	74	74	74				
56	..	..	..	75	76	77	77	77	78	78	80			
57	..	..	..	..	79	80	81	81	82	83	83			
58	..	..	..	..	83	84	84	85	85	86	87			
59	..	..	..	..	..	87	88	89	89	90	90	90		
60	..	..	..	..	..	91	92	92	93	94	95	96		
61	..	..	..	..	..	..	95	96	97	99	100	103	106	
62	..	..	..	..	..	..	100	101	102	103	104	107	111	116
63	..	..	..	..	..	..	105	106	107	108	110	113	118	123
64	..	..	..	..	..	..	..	109	111	113	115	117	121	126
65	..	..	..	..	..	..	..	114	117	118	120	122	127	131
66	..	..	..	..	..	..	..	..	119	122	125	128	132	136
67	..	..	..	..	..	..	..	..	124	128	130	134	136	139
68	..	..	..	..	..	..	..	...	...	134	134	137	141	143
69	..	..	..	..	..	..	..	...	...	137	139	143	146	149

The above table, published by the Bureau of Publications, Teachers College, Columbia University, was prepared by Drs. Bird T. Baldwin and Thomas D. Wood.

Table 91.—*Height and Weight Tables for Girls*

4 to 18 Years

Average weight in pounds at successive heights (left column) and ages (top row)

Hgt. (In.)	5 yrs.	6 yrs.	7 yrs.	8 yrs.	9 yrs.	10 yrs.	11 yrs.	12 yrs.	13 yrs.	14 yrs.	15 yrs.	16 yrs.	17 yrs.	18 yrs.
38	33	33												
39	34	34												
40	36	36	36											
41	37	37	37											
42	39	39	39											
43	41	41	41	41										
44	42	42	42	42										
45	45	45	45	45	45									
46	47	47	47	48	48									
47	49	50	50	50	50	50								
48	..	52	52	52	52	53	53							
49	..	54	54	55	55	56	56							
50	..	56	56	57	58	59	61	62						
51	..	..	59	60	61	61	63	65						
52	..	..	63	64	64	64	65	67						
53	..	..	66	67	67	68	68	69	71					
54	..	..	..	69	70	70	71	71	73					
55	..	..	..	72	74	74	74	75	77	78				
56	..	..	..	..	76	78	79	81	83	85				
57	..	..	..	..	80	82	82	82	84	88	92			
58	..	..	..	..	..	84	86	86	88	93	96	101		
59	..	..	..	..	..	87	90	90	92	96	100	103	104	
60	..	..	..	..	..	91	95	95	97	101	105	108	109	111
61	..	..	..	..	..	..	99	100	101	105	108	112	113	116
62	..	..	..	..	..	..	104	105	106	109	113	115	117	118
63	..	..	..	..	..	..	...	110	110	112	116	117	119	120
64	..	..	..	..	..	..	...	114	115	117	119	120	122	123
65	..	..	..	..	..	..	...	118	120	121	122	123	125	126
66	..	..	..	..	..	..	...	...	124	124	125	128	129	130
67	..	..	..	..	..	..	...	...	128	130	131	133	133	135
68	..	..	..	..	..	..	...	...	131	133	135	136	138	138
69	..	..	..	..	..	..	...	...	...	135	137	138	140	142

The above weight table, published by the Bureau of Publications, Teachers College, Columbia University, was prepared by Drs. Bird T. Baldwin and Thomas D. Wood.

TABLE 92.—*Height and Weight Tables for Boys*
Birth to 4 Years

Age	Average Height		Average Weight	
	In.	Cm.	Lbs.	Kg.
At birth	20.6	52.3	7.48	3.39
Under 1 month	21⅛	53.6	9⅛	4.13
1 month under 2	22½	57.1	10⅞	4.93
2 months under 3	23⅝	60.1	12⅝	5.73
3 months under 4	24½	62.2	14⅛	6.40
4 months under 5	25⅜	64.4	15⅜	6.97
5 months under 6	26⅛	66.3	16¼	7.37
6 months under 7	26¾	67.9	17½	7.94
7 months under 8	27¼	69.2	18¼	8.27
8 months under 9	27¾	70.4	19	8.61
9 months under 10	28¼	71.7	19⅝	8.90
10 months under 11	28⅝	72.7	20¼	9.19
11 months under 12	29	73.6	20¾	9.41
1 year	29½	74.9	21⅜	9.69
2 years	33⅝	85.5	26⅝	12.09
3 years	36⅝	93.0	30¾	13.94
4 years	38	96.5	34	15.40

The above weight table, published by the Bureau of Publications, Teachers College, Columbia University, was prepared by Drs. Bird T. Baldwin and Thomas D. Wood.

TABLE 93.—*Height and Weight Table for Girls*
Birth to 4 Years

Age	Average Height		Average Weight	
	In.	Cm.	Lbs.	Kg.
At birth	20.5	52.0	7.2	3.25
Under 1 month	20⅞	53.0	8⅝	3.91
1 month under 2	21⅞	55.5	10⅛	4.60
2 months under 3	23⅛	58.6	11¾	5.33
3 months under 4	24	60.9	13	5.90
4 months under 5	24⅞	63.2	14¼	6.46
5 months under 6	25½	64.7	15⅜	6.97
6 months under 7	26⅛	66.3	16¼	7.37
7 months under 8	26¾	67.9	17⅛	7.77
8 months under 9	27¼	69.2	17¾	8.05
9 months under 10	27⅝	70.2	18½	8.39
10 months under 11	28⅛	71.3	19	8.62
11 months under 12	28½	72.3	19½	8.85
1 year	28⅞	73.3	20	9.07
2 years	33⅛	84.0	25⅛	11.40
3 years	36¼	92.0	29½	13.38
4 years	38	96.5	33	14.96

The above weight table, published by the Bureau of Publications, Teachers College, Columbia University, was prepared by Drs. Bird T. Baldwin and Thomas D. Wood.

TABLE 94.—*Quick-Reference Conversion Table*

Pounds to Kilograms

1 pound = 0.4536 kilograms
1 kilogram = 2.2046 pounds

The numerical values in the body of the table are the equivalent weights in kilograms of the amounts in pounds listed at the top and side. For example, to find the equivalent weight in kilograms of 126 pounds, read down the extreme left column to 120, then read across on that line to the column headed 6. The value found these, 57.1, is the weight in kilograms equivalent to 126 pounds.

	0	1	2	3	4	5	6	7	8	9
0		0.4	0.9	1.3	1.8	2.2	2.7	3.1	3.6	4.0
10	4.5	4.9	5.4	5.8	6.3	6.8	7.2	7.7	8.1	8.6
20	9.0	9.5	9.9	10.4	10.8	11.3	11.7	12.2	12.7	13.1
30	13.6	14.0	14.5	14.9	15.4	15.8	16.3	16.7	17.2	17.6
40	18.1	18.5	19.0	19.5	19.9	20.4	20.8	21.3	21.7	22.2
50	22.6	23.1	23.5	24.0	24.4	24.9	25.4	25.8	26.3	26.7
60	27.2	27.6	28.1	28.5	29.0	29.4	29.9	30.3	30.8	11.2
70	31.7	32.2	32.6	33.1	33.5	34.0	34.4	34.9	35.3	35.8
80	36.2	36.7	37.1	37.6	38.1	38.5	39.0	39.4	39.9	40.3
90	40.8	41.2	41.7	42.1	42.6	43.0	43.5	43.9	44.4	44.9
100	45.3	45.8	46.2	46.7	47.1	47.6	48.0	48.5	48.9	49.4
110	49.8	50.3	50.8	51.2	51.7	52.1	52.6	53.0	53.2	53.9
120	54.4	54.8	55.3	55.7	56.2	56.7	57.1	57.6	58.0	58.5
130	58.9	59.4	59.8	60.3	60.7	61.2	61.6	62.1	62.5	63.0
140	63.5	63.9	64.4	64.8	65.3	65.7	66.2	66.6	67.1	67.5
150	68.0	69.4	68.9	69.4	69.8	70.3	70.7	71.2	71.6	72.1
160	72.5	73.0	73.4	73.9	74.3	74.8	75.2	75.7	76.2	76.6
170	77.1	77.5	78.0	78.4	78.9	79.3	79.8	80.2	80.7	81.1
180	81.6	82.1	82.5	83.0	83.4	83.9	84.3	84.8	85.2	85.7
190	86.1	86.6	87.0	87.5	87.9	88.4	88.9	89.3	89.8	90.2
200	90.7	91.1	91.6	92.0	92.5	92.9	93.4	93.8	94.3	94.8

TABLE 95.—*Quick-Reference Conversion Table*

Inches to Centimeters

1 inch = 2.54 centimeters
1 centimeter = .3937 inch

The numerical values in the body of the table are the equivalent lengths in centimeters of the values in inches listed at the top and side. For example, to find the equivalent length in centimeters of 36 inches, read down the extreme left column to 30, then read across on that line to the column headed 6. The value found there, 91.44, is the length in centimeters of 36 inches.

	0	1	2	3	4	5	6	7	8	9
0		2.54	5.08	7.62	10.16	12.70	15.24	17.78	20.32	22.86
10	25.40	27.96	30.48	33.02	35.56	38.10	40.64	43.18	45.72	48.26
20	50.80	53.34	55.88	58.42	60.96	63.50	66.04	68.58	71.12	73.66
30	76.20	78.74	81.28	83.82	86.36	88.90	91.44	93.98	96.52	99.06
40	101.60	104.14	106.68	109.22	111.76	114.30	116.84	119.38	121.92	124.46
50	127.00	129.54	132.08	134.62	137.16	139.70	142.24	144.78	147.32	149.86
60	152.40	154.90	157.48	160.02	162.56	165.10	167.64	170.18	172.72	175.26
70	177.80	180.34	182.88	185.42	187.96	190.50	193.04	195.58	198.12	200.66
80	203.20	205.74	208.28	210.82	213.36	215.90	218.44	220.98	223.52	226.06
90	228.60	231.13	233.68	236.22	238.76	241.30	243.84	246.38	248.92	251.46
100	254.00	256.54	259.08	261.62	264.16	266.70	269.24	271.78	274.32	276.86

TABLE 96.—*Quick-Reference Conversion Tables*

Minims to Cubic Centimeters

1 minim = 0.06 cubic centimeter
1 cc. = 16.67 minims

The numerical values in the body of the table are equivalent volumes in cubic centimeters of the amounts in minims listed at the top and side. For example, to find the equivalent volumes in cubic centimeters of 21 minims read down the extreme left column to 20 then read across on that line to the column headed 1. The value found there, 1.26, is the volume in cubic centimeters equivalent to 21 grams.

	0	1	2	3	4	5	6	7	8	9
0		0.06	0.12	0.18	0.24	0.30	0.36	0.42	0.48	0.54
10	0.60	0.66	0.72	0.78	0.84	0.90	0.96	1.02	1.08	1.14
20	1.20	1.26	1.32	1.38	1.44	1.50	1.56	1.62	1.68	1.74
30	1.80	1.86	1.92	1.98	2.04	2.10	2.16	2.22	2.28	2.34
40	2.40	2.46	2.52	2.58	2.64	2.70	2.76	2.82	2.88	2.94
50	3.00	3.06	3.12	3.18	3.24	3.30	3.36	3.42	3.48	3.54
60	3.60	3.66	3.72	3.78	3.84	3.90	3.96	4.02	4.08	4.14

Ounces to Grams

1 ounce = 28.35 grams
1 gram = 0.03527 ounces

The numerical values in the body of the table are the equivalent weights in grams of the amounts in ounces listed at the top and side. For example, to find the equivalent weight in grams of 35 ounces, read down the extreme left column to 30, then read across on that line to the column headed 5. The value found there, 992.25, is the weight in grams equivalent to 35 ounces.

	0	1	2	3	4	5	6	7	8	9
0		28.35	56.70	85.05	113.40	141.75	170.10	198.45	226.80	255.15
10	283.5	311.85	340.20	368.55	396.90	425.25	453.60	481.95	510.30	538.65
20	567.0	595.35	623.70	652.05	680.40	708.75	737.10	765.45	793.80	822.15
30	850.5	878.85	907.20	935.55	963.90	992.25	1020.60	1048.95	1077.30	1105.65
40	1134.0	1162.35	1190.70	1219.05	1247.40	1275.75	1304.10	1332.45	1360.80	1389.15
50	1477.5	1445.85	1474.20	1502.55	1530.90	1559.21	1587.60	1615.95	1644.30	1672.65

TABLE 97.—*Household Weight and Capacity Measures for Foods*[1313]

Food	Common Measures	Household Equivalent
Bread	1 loaf (16 ounces)	5 cups soft crumbs
Butter	1 pound	2 cups
Cheese		
American	½ pound	2½ cups, grated
cream	3 ounces	6⅔ tablespoonfuls
Chocolate		
cake	1 ounce	1 square
ground	1 ounce	4 tablespoonfuls
Cornmeal	1 pound	3 cups
Eggs	1 medium size	2 ounces
whites	7 to 10	1 cup
yolks	11 to 14	1 cup
Flour		
cake, sifted	1 pound	4½ cups
bread	1 pound	4 cups
graham	1 pound	3½ cups
rye	1 pound	5 cups
Lemon		
juice	1 medium size	3 tablespoonfuls
rind, grated	1 medium size	3 teaspoonfuls
Orange		
juice	1 medium size	½ cup
rind, grated	1 medium size	2 tablespoonfuls
Rice	1 pound ½ cup, raw	2 cups 2 cups, cooked
Suet	2½ ounces	1 cup, chopped
Sugar		
brown	1 pound	2 cups, firmly packed
confectioners	1 pound	3½ cups
granulated	1 pound	2¼ cups
Salt	1 ounce	2 tablespoonfuls
Pepper	1 ounce	3 tablespoonfuls
Cornstarch	1 ounce	3 tablespoonfuls
Cinnamon	1 ounce	4 tablespoonfuls
Cloves	1 ounce	4 tablespoonfuls
Mace	1 ounce	4 tablespoonfuls
Curry powder	1 ounce	4 tablespoonfuls
Mustard	1 ounce	4 tablespoonfuls
Thyme	1 ounce	4 tablespoonfuls
Marshmallows	¼ pound	16 marshmallows
Almonds (in shell)	1 pound	2 cups, chopped
Peanuts (in shell)	1 pound	2 cups, chopped
Pecans (in shell)	1 pound	2 cups, chopped
Walnuts (in shell)	4 ounces	1 cup, chopped

[1313] WOHL, M. G. and WILLARD, J. A.: A Guide to Practical Nutrition. Philadelphia: The Philadelphia County Medical Society, 1943.

TABLE 98.—*Nutritive Values of Meats* and Viscera (Edible Portion)*

Food	Average Portion			Percentage by Weight			Milligrams per 100 Gm.		Vitamin Content per 100 Grams			
	Measure	Weight in grams	Total calories	Protein	Carbohydrate other than fiber	Fat	Sodium	Chloride	A I.U.	Thiamine (mg.)	Riboflavin (mg.)	Ascorbic acid (mg.)
Bacon, lean........	4 slices	28	149	12.2	1.4	53.0	See footnote	See footnote	—	0.20	0.14	—
Beef, lean..........	¼ lb.	115	288	18.6	0.0	16.0			21	0.08	0.21	—
Beef tongue........	5 slices	75	170	17.4	0.4	11.0			—	—	—	—
Ham, lean, fresh...	¼ lb.	115	315	19.5	0.3	25.0			—	1.18	0.27	—
Lamb chops........	2 chops	115	406	21.7	0.7	29.9			—	0.20	0.30	—
Mutton, leg........	¼ lb.	115	216	19.8	0.0	12.4			—	—	—	—
Pork chops.........	2 chops	115	302	17.9	0.0	18.0			+	1.45	0.22	—
Pork sausage......	2 links	35	156	10.8	0.0	44.8			—	0.26	0.15	
Veal chops.........	2 chops	115	186	19.7	0.0	8.0			—	0.18	0.31	—
Veal cutlet.........	¼ lb.	115	168	19.9	0.0	6.0			—	0.18	0.30	—
Beef brains........	¼ lb.	115	144	10.5	1.4	8.8			—	—	—	—
Beef heart.........	¼ lb.	115	118	16.9	0.7	3.7			20	0.50	0.89	2
Beef kidney........	1 c.	115	155	15.0	0.9	8.1			1,100	—	—	—
Beef liver..........	¼ lb.	115	149	19.7	6.0	3.2			27,500	0.32	2.54	31
Beef sweetbreads..	¼ lb.	115	195	14.4	0.0	19.0			—	—	—	—
Tripe..............	¼ lb.	115	106	19.1	0.0	2.0			—	—	—	—
Gelatin, dried......	1 T.	9	31	85.6	0.0	0.1			—	—	—	—

* Average meat is estimated to contain 421 mg. of sodium and 378 mg. of chloride per 100 grams of protein. No reliable figures for viscera are available.

Symbols:

T. = tablespoon	— = none present or insufficient data
c. = cup	+ = moderate quantity

Table 99.—*Nutritive Values of Poultry* and Eggs (Edible Portion)*

Food	Average Portion			Percentage by Weight			Milligrams per 100 Gm.		Vitamin Content per 100 Grams			
	Measure	Weight in grams	Total calories	Protein	Carbohydrate other than fiber	Fat	Sodium	Chloride	A (I.U.)	Thiamine (mg.)	Riboflavin (mg.)	Ascorbic acid (mg.)
Chicken	¼ lb.	115	141	21.1	0.0	4.5	See footnote	See footnote	5	0.10	0.20	4
Duck	¼ lb.	115	180	21.4	0.0	8.2			++	0.13	0.41	—
Goose	¼ lb.	115	173	22.3	0.0	7.1			—	—	—	—
Turkey	¼ lb.	115	176	24.0	0.0	6.7			+	0.13	0.24	—
Egg white	1 white	35	16	10.8	0.8	0.0	156	155	—	—	0.30	—
Egg yolk	1 yolk	17	60	16.3	0.7	31.9	75	94	2,800	0.42	0.35	—
Egg, whole	1, shell removed	52	82	12.8	0.7	11.5	143	106	1,000	0.14	0.37	—

* Average poultry is estimated to contain 421 mg. of sodium and 378 mg. of chloride per 100 grams of protein.

Symbols:

— = none present or insufficient data
+ = moderate quantity
++ = high

TABLE 100.—*Nutritive Values of Fish* and Shellfish (Edible Portion)*

Food	Average Portion			Percentage by Weight			Milligrams per 100 Gm.		Vitamin Content per 100 Grams			
	Measure	Weight in grams	Total calories	Protein	Carbohydrate other than fiber	Fat	Sodium	Chloride	A (I.U.).	Thiamine (mg.)	Riboflavin (mg.)	Ascorbic acid (mg.)
Bluefish	1 fish filet	115	133	20.5	0.0	4.0	See footnote	See footnote	−	+	+	−
Codfish	¼ lb. filet	115	79	16.5	0.0	0.4			10	0.12	0.16	−
Haddock	¼ lb. filet	115	81	17.2	0.0	0.3			7	0.12	0.16	−
Halibut	¼ lb. filet	115	137	18.6	0.0	5.2			+	0.12	0.18	−
Herring	1 filet	115	154	19.0	0.0	6.7			200	0.12	1.0	−
Mackerel	1 filet	115	207	18.7	0.0	12.0			150	0.12	0.66	−
Salmon	1 c. canned	115	246	17.4	0.0	16.5			270	0.12	0.22	9
Sardines in oil	4 sardines	50	104	25.7	1.2	11.0			140	0.09	0.62	−
Tuna in oil	½ c. canned	57	111	24.2	0.0	10.8			200	+	+	−
Whitefish	¼ lb. filet	115	170	22.9	0.0	6.5			+	0.09	++	−
Clams	9	115	87	12.8	3.4	1.4	705	1,220	200	0.02	0.01	30
Crabs	⅔ c.	115	92	16.1	0.6	1.6			++	0.14	0.35	13
Lobster	⅔ c. canned	115	95	16.2	0.5	1.9			−	0.15	0.13	5
Oysters	6	115	92	9.8	5.9	2.0	459	590	210	0.20	0.46	3
Scallops	⅔ c.	115	84	14.8	3.4	0.1			−	++	−	3
Shrimp	8	65	72	25.4	0.2	1.0			+	0.09	0.16	3

* Average fish is estimated to contain 373 mg. of sodium and 528 mg. of chloride per 100 grams of protein.

Symbols:

− = none present or insufficient data
+ = moderate quantity
++ = high

TABLE 101.—*Nutritive Values of Dairy Products*

Food	Average Portion			Percentage by Weight			Milligrams per 100 Gm.		Vitamin Content per 100 Grams			
	Measure	Weight in grams	Total calories	Protein	Carbohydrate	Fat	Sodium	Chloride	A (I.U.)	Thiamine (mg.)	Riboflavin (mg.)	Ascorbic acid (mg.)
Butter, unsalted...	1″ x 1″ x ½″	10	80	1.0	—	85.0	276	414	2,400	—	—	—
Butter, salted......	1″ x 1″ x ½″	10	80	1.0	—	85.0	788	1,212	2,400	—	—	—
Buttermilk.........	1 c.	240	85	3.3	4.5	0.4	64	99	20	0.02	0.18	1
Cheese, American..	1½″ x 1½″ x 1¼″	25	120	21.2	1.4	37.0	606	880	1,430	0.04	0.48	—
Cheese, cottage....	¼ c.	55		20.9	4.3	1.0	200	150	70	0.01	0.13	—
Cheese, cream, unsalted............	2 T.	30	120	10.0	0.2	38.0	80	120	2,100	—	180	—
Cheese, cream, salted............	2 T.	30	120	10.0	0.2	38.0	476	714	2,100	—	180	—
Cream, sour, 40%..	1 T.	15	29	2.5	2.5	40.0	—	—	2,200	—	—	—
Cream, 20%........	1 T.	15	31	3.0	4.0	20.0	35	80	1,200	0.03	0.13	—
Milk, condensed, sweetened.......	2 T.	30	98	8.1	54.8	8.4	134	280	430	0.05	0.42	1
Milk, evaporated..	1 T.	15	20	6.7	10.1	8.2	—	—	410	0.05	0.36	1
Milk, goat's.......	1 c.	240	170	4.0	3.8	4.2	140	210	170	—	—	—
Milk, human......	3 oz.	100	68	1.4	7.2	3.7	24	35	350	—	—	—
Milk, skimmed....	1 c.	240	12	3.6	4.7	0.7	74	110	3	0.10	0.28	2
Milk, whole.......	1 c.	240	165	3.5	5.0	3.9	51	106	170	0.04	0.18	1

Symbols:
T. = tablespoon — = none present or insufficient data
c. = cup

TABLE 102.—*Nutritive Values of Vegetables (Edible Portion)*

Food	Average Portion			Percentage by Weight			Milligrams per 100 Gm.		Vitamin Content per 100 Grams			
	Measure	Weight in grams	Total calories	Protein	Carbohydrate other than fiber	Fat	Sodium	Chloride	A (I.U.)	Thiamine (mg.)	Riboflavin (mg.)	Ascorbic acid (mg.)
Artichokes	1 heart, edible leaf portion	100	50	2.9	8.7	0.4	–	–	300	0.250	+	22
Asparagus	6 stalks	100	23	2.2	3.2	0.2	7	39	970	0.19	0.12	63
Beans, dried	2 T. shelled	28	94	22.0	58.2	1.5	97	32	100	0.52	0.30	–
Beans, snap	1 c. stringless	100	37	2.4	6.3	0.2	19	24	600	0.08	0.12	21
Beans, green Lima	⅔ c. shelled	100	125	7.5	22.0	0.8	88	9	600	0.08	0.12	21
Beets	⅔ c.	100	42	1.6	8.7	0.1	93	58	–	0.02	0.04	15
Beet greens	1 c.	100	28	2.0	4.2	0.3	–	–	8,000	++	0.50	33
Broccoli	1 c.	100	32	3.3	4.2	0.2	–	–	2,540	0.09	0.24	99
Brussels sprouts	6	100	53	4.4	7.6	0.5	4	40	350	0.13	–	120
Cabbage	¾ c. shredded as slaw	57	14	1.4	4.3	0.2	27	24	40	0.08	0.05	50
Carrots	1 large, scraped	100	40	1.2	8.2	0.3	101	36	15,000	0.06	0.06	5
Cauliflower	1 c.	100	27	2.4	4.0	0.2	68	50	140	0.15	0.13	70
Celery, blanched	2 stalks	40	8	1.3	3.0	0.2	84	156	–	0.04	0.04	9
Chard, leaves	1½ c.	100	30	2.6	4.0	0.4	86	39	9,000	0.05	0.12	30
Corn, canned	½ c.	115	109	2.5	19.2	0.9	–	–	–	–	–	–
Corn, green (yellow)	½ c. cut from cob	100	104	3.7	19.7	1.2	40	14	240	0.13	0.12	10
Cucumbers	10 slices, pared	57	7	0.7	2.2	0.1	10	30	200	0.04	0.05	10
Dandelion greens	1 c.	100	45	2.7	7.0	0.7	168	99	12,000	–	+	100

TABLE 102.—*Continued*

Food	Average Portion			Percentage by Weight			Milligrams per 100 Gm.		Vitamin Content per 100 Grams			
	Measure	Weight in grams	Total caloies	Protein	Carbohydrate other than fiber	Fat	Sodium	Chloride	A (I.U.)	Thiamine (mg.)	Riboflavin (mg.)	Ascorbic acid (mg.)
Eggplant	2 slices, pared	100	25	1.1	4.6	0.2	10	24	35	0.04	0.03	10
Endive	½ head	45	9	1.6	3.2	0.2	109	167	3,600	0.06	0.20	13
Escarole (chicory)	¼ head	16	3	1.6	2.1	0.3	—	—	10,000	0.02	0.09	10
Kale	1 c. leaves	100	45	3.9	6.0	0.6	—	—	10,000	0.19	0.40	125
Kohlrabi	½ c.	100	32	2.1	5.6	0.1	50	53	—	0.05	0.07	—
Leeks	2 bulbs	57	23	2.5	6.6	0.4	81	24	+	0.15	+	20
Lentils, dried	2 T.	28	94	24.7	56.6	1.0	62	50	+	0.50	0.40	—
Lettuce	¼ head	75	12	1.2	2.3	0.2	27	74	200	0.09	0.04	10
Marrow, vegetable	⅝ c.	100	17	0.5	3.4	0.1	—	14	30	0.04	—	11
Mushrooms	7	100	30	3.9	3.1	0.2	27	21	+	0.12	0.04	8
Mustard greens	1 c. leaves	100	25	2.3	3.2	0.3	—	—	11,000	0.14	0.37	180
Okra	5 pods	50	17	1.8	6.4	0.2	43	—	400	0.13	0.10	27
Onions	1	50	23	1.4	9.5	0.2	16	21	—	0.03	0.02	20
Parsley	1 sprig	1	...	3.7	7.2	1.0	—	—	5,000	0.08	—	140
Parsnips	½ large, scraped	100	75	1.5	16.0	0.5	4	30	50	0.12	0.08	15
Peas, dried	2 T.	28	92	23.8	54.8	1.4	104	35	180	0.54	0.18	—
Peas, green	¾ c. shelled	100	92	6.7	15.5	0.4	13	24	700	0.30	0.20	25
Peppers, green	1 empty pod	100	24	1.2	4.3	0.2	—	13	500	0.06	0.04	180
Potatoes, sweet	1 pared	145	175	1.8	26.9	0.7	39	94	7,200	0.10	0.07	33
Potatoes, white	1 pared	120	101	2.0	18.7	0.1	21	38	40	0.15	0.05	18
Pumpkins	½ c. seeded, rind removed	100	31	1.2	6.0	0.2	65	36	2,500	0.05	0.04	10
Radishes	5	35	7	1.2	3.5	0.1	69	54	—	0.03	0.03	26
Rhubarb	1 c. stems	100	15	0.5	3.1	0.1	5	36	100	0.02	—	15

TABLE 102.—*Concluded*

Food	Average Portion			Percentage by Weight			Milligrams per 100 Gm.		Vitamin Content per 100 Grams			
	Measure	Weight in grams	Total calories	Protein	Carbohydrate other that fiber	Fat	Sodium	Chloride	A (I.U.)	Thiamine (mg.)	Riboflavin (mg.)	Ascorbic acid (mg.)
Rutabaga.........	¾ c. scraped	100	36	1.1	7.6	0.1	83	58	25	0.07	.06	30
Spinach...........	1 c. leaves	100	22	2.3	2.6	0.3	125	74	8,400	0.10	0.20	75
Squash, summer..	1 c. seeded, rind removed	100	17	0.6	3.4	0.1	2	—	1,600	0.04	0.08	23
Squash, winter...	1 c. seeded, rind removed	100	38	1.5	7.4	0.3	4	—	1,700	0.04	0.08	18
Tomatoes.........	1 small, cored	100	20	1.0	3.4	0.3	10	34	1,200	0.08	0.04	27
Turnips...........	¾ c. pared	100	30	1.1	6.0	0.2	58	41	15	0.06	0.05	33
Turnip greens....	1 c. leaves	100	32	2.9	4.2	0.4	82	168	10,000	0.14	0.37	120
Water cress.......	2½ c. leaves	100	21	1.7	2.8	0.3	99	61	4,000	0.12	0.25	60

Symbols:
T. = tablespoon
c. = cup
— = none present or insufficient data
+ = moderate quantity
++ = high

TABLE 103.—*Nutritive Values of Fruits (Edible Portion)*

Food	Average Portion			Percentage by Weight			Milligrams per 100 Gm.		Vitamin Content per 100 Grams			
	Measure	Weight in grams	Total calories	Protein	Carbohydrate other than fiber	Fat	Sodium	Chloride	A (I.U.)	Thiamine (mg.)	Riboflavin (mg.)	Ascorbic acid (mg.)
Apples	1 large, cored	150	90	0.3	13.9	0.4	11	5	80	0.04	0.02	6
Apricots	4 halves, stoned	100	54	1.0	12.3	0.1	38	2	2,000	0.03	0.07	7
Avocados	½ pear, pared, stoned	100	179	2.0	4.0	17.2	16	6	230	0.10	0.15	20
Bananas	1 small, peeled	100	96	1.2	22.4	0.2	34	12	400	0.06	0.09	18
Blackberries	1 c.	100	46	1.2	7.8	1.1	7	10	83	0.04	—	10
Blueberries	⅔ c.	100	63	0.6	13.9	0.6	16	8	100	0.04	0.02	15
Cherries	18 stoned	100	67	1.1	14.5	0.5	23	14	1,200	0.05	0.06	12
Cranberries	1 c.	100	48	0.4	9.9	0.7	7	5	40	—	—	15
Currants, fresh	1 c.	100	48	1.6	9.5	0.4	7	6	400	0.03	—	100
Dates	4 stoned	30	92	2.2	73.0	0.6	55	22	210	0.07	0.03	—
Figs, dried	1½	30	83	4.0	62.6	1.2	46	43	75	0.07	0.80	—
Gooseberries	⅔ c.	100	37	0.8	7.6	0.4	38	11	—	0.01	—	25
Grapefruit	½ c. juice	100	43	0.5	9.8	0.2	4	5	10	0.07	0.02	42
Grapes	1 bunch, seeded	100	76	1.4	14.4	1.4	15	5	50	0.07	0.06	5
Lemons	½ c. juice	100	40	0.9	7.8	0.6	4	2	—	0.02	—	36
Limes	½ c. juice	100	39	0.8	8.6	0.1	62	39	—	0.02	0.02	36
Loganberries	1 c.	100	64	1.0	13.6	0.6	3	16	—	0.03	—	35
Muskmelons	½ seeded, rind removed	200	52	0.6	5.4	0.2	61	41	2,400	0.05	0.07	25
Nectarines	2 pared, stoned	100	65	0.5	15.6	0.1	9	5	2,800	0.07	—	25
Oranges	½ c. juice	100	48	0.9	10.6	0.2	12	6	250	0.07	0.03	48
Peaches, fresh	1 large, pared, stoned	100	49	0.5	11.4	0.1	22	4	1,200	0.02	0.06	8
Pears, fresh	2 halves, cored, pared	100	64	0.7	14.4	0.4	16	11	50	0.06	0.05	5

TABLE 103.—*Continued*

Food	Average Portion			Percentage by Weight			Milligrams per 100 Gm.		Vitamin Content per 100 Grams			
	Measure	Weight in grams	Total calories	Protein	Carbohydrate other than fiber	Fat	Sodium	Chloride	A (I.U.)	Thiamine (mg.)	Riboflavin (mg.)	Ascorbic acid (mg.)
Persimmons	1 small, seeded	100	135	0.8	32.0	0.4	11	2	2,600	—	—	18
Pineapples, fresh	2 slices, canned	100	57	0.4	13.3	0.2	16	51	200	0.09	0.05	38
Plums	3 stoned	100	54	0.7	12.4	0.2	19	2	360	—	0.04	5
Pomegranates	½ seeded	100	74	0.6	17.4	0.2	85	3	—	—	0.10	6
Prunes, dried	4 stewed, stoned	37	108	2.3	69.4	0.6	19	17	2,000	0.08	0.10	6
Quinces	1 boiled, as a sauce	100	51	0.3	12.1	0.1	3	2	—	—	—	9
Raisins	⅓ c. seeded and seedless	45	131	2.3	69.5	0.5	133	82	100	0.10	0.13	3
Raspberries, black	⅞ c.	100	69	1.5	12.1	1.6	—	—	100	0.02	—	30
Raspberries, red	⅞ c.	100	56	1.1	11.6	0.6	2	22	130	0.02	—	30
Strawberries	12 hulled	100	36	0.8	6.9	0.6	50	6	50	0.03	0.03	60
Tangerines	2 peeled, seeded	100	46	0.8	9.9	0.3	2	2	30	0.07	0.04	40
Watermelon	1 slice, seeded	200	58	0.5	6.3	0.2		8.0	500	60	35	7

Symbols:

c. = cup — = none present or insufficient data

TABLE 104.—*Nutritive Values of Cereals and Cereal Products*

Food	Average Portion			Percentage by Weight			Milligrams per 100 Gm.		Vitamin Content per 100 Grams			
	Measure	Weight in grams	Total calories	Protein	Carbohydrate other than fiber	Fat	Sodium	Chloride	A (I.U.)	Thiamine (mg.)	Riboflavin (mg.)	Ascorbic acid (mg.)
Barley, pearled	3 T.	30	107	8.2	78.3	1.0	37	16	—	0.05	—	—
Bread, rye	3 slices	50	125	8.9	49.2	2.0	701	1,025	—	0.21	—	—
Bread, white	2 slices	50	130	8.5	52.0	2.0	394	607	—	0.06	—	—
Bread, whole wheat	2 slices	50	129	9.5	47.0	3.5	394	607	—	0.24	0.15	—
Corn meal, yellow	3 T.	30	107	9.1	71.9	3.7	39	146	110	0.18	0.07	—
Farina	3 T.	30	107	11.5	75.8	1.0	65	76	—	0.06	0.06	—
Flour, buckwheat	2 T.	22	77	6.3	79.3	1.1	27	12	—	0.13	—	—
Flour, rye	2 T.	18	64	8.9	77.4	0.9	19	55	—	—	—	—
Flour, soy bean 7% fat	2 T.	18	68	37.3	9.5	20.2	—	—	110	0.60	0.40	—
Flour, white	2 T.	17	60	10.8	75.6	0.9	60	74	—	0.09	—	—
Flour, enriched min.	2 T.	17	60	10.8	75.6	0.9	60	74	—	0.44	0.26	—
Flour, enriched max.	2 T.	17	60	10.8	75.6	0.9	60	74	—	—	—	—
Hominy grits	¼ c.	50	178	8.5	78.5	0.8	20	46	—	0.13	0.12	—
Macaroni or spaghetti	¼ c.	28	101	13.0	73.5	1.4	8	73	—	0.10	0.06	—
Oatmeal	¼ c.	25	98	14.2	67.0	7.4	62	69	—	0.63	0.14	—
Rice, unpolished	3 T.	30	106	7.5	77.1	1.7	—	—	—	0.25	0.15	—
Rice, white	2 T.	28	98	7.6	79.2	0.3	25	54	—	0.06	0.06	—
Tapioca	¼ c.	40	140	0.6	86.3	0.2	—	18	—	—	—	—
Wheat bran	1 c.	28	87	16.0	50.2	5.2	154	90	—	1.30	0.11	—
Wheat germ	2 T.	20	76	25.2	47.0	10.0	722	70	—	3.00	0.35	—
Wheat, whole	2 T.	20	72	11.7	74.0	2.0	39	68	—	0.49	0.13	—

Symbols:

T. = tablespoon

c. = cup

— = none present or insufficient data

Table 105.—*Nutritive Values of Nuts (Edible Portion)*

Food	Average Portion			Percentage by Weight			Milligrams per 100 Gm.		Vitamin Content per 100 Grams			
	Measure	Weight in grams	Total calories	Protein	Carbohydrate other than fiber	Fat	Sodium	Chloride	A (I.U.)	Thiamine (mg.)	Riboflavin (mg.)	Ascorbic acid (mg.)
Almonds	12 nuts	14	88	18.6	16.9	54.1	5.8	37.0	580	0.10	0.24	—
Brazil nuts	2 nuts	14	96	14.4	8.9	65.9	1.5	61.0	10	0.34	++	—
Butternuts	4 nuts	14	95	23.7	8.4	61.2	—	—	+	++	—	—
Cashew	10 nuts	14	85	19.6	25.4	47.2	—	—	+	+	0.07	—
Chestnuts, fresh	3 nuts, skin removed	14	26	2.8	40.4	1.5	10.9	6.0	—	0.08	+	—
Coconut, fresh	1 inch square	10	60	5.7	27.9	50.6	16.5	120.0	+	0.03	0.04	—
Hazelnuts (filberts)	10 nuts	14	92	12.7	14.3	60.9	—	67.0	440	0.22	++	—
Hickory nuts	12 nuts	14	99	13.9	11.0	67.4	—	—	—	++	++	—
Peanuts	16 nuts, skin removed	14	83	26.9	21.2	44.2	5.6	56.0	360	0.22	0.20	—
Pecans	12 meats	14	103	9.4	10.8	73.0	—	—	400	0.35	0.10	—
Walnuts, black	12 meats	14	93	18.3	16.8	58.2	—	—	130	0.11	—	—
Walnuts, English	12 meats	14	97	15.0	13.5	64.4	2.7	40.0	100	0.13	+	—

Symbols:
— = none present or insufficient data
+ = moderate quantity
++ = high

TABLE 106.—*Miscellaneous Foods*

Food	Average Portion			Percentage by Weight			Milligrams per 100 Gm.		Vitamin Content per 100 Grams			
	Measure	Weight in grams	Total calories	Protein	Carbohydrate other than fiber	Fat	Sodium	Chloride	A (I.U.).	Thiamine (mg.)	Riboflavin (mg.)	Ascorbic acid (mg.)
Corn syrup	1 T.	21	62	—	74.0	—	—	—	—	—	0.02	—
Maple syrup	1 T.	25	64	—	64.0	—	10	10	—	—	—	—
Sugar												
granulated (sucrose)	2 t.	8	32	—	99.5	—	—	—	—	—	—	—
brown	2 t.	5	19	0.4	99.5	—	—	—	—	—	—	—
Honey	1 T.	25	80	0.3	79.5	—	1	29	—	0.01	0.07	2
Molasses	2 t.	15	40	2.1	69.3	—	19	317	—	0.02	0.02	—
Marmalade, orange	1 T.	25	85	0.6	84.5	0.1	—	7	—	0.02	0.02	8
Preserves, miscellaneous, average	1 T.	25	254	0.4	63.0	0.1	—	—	10	0.01	0.02	—
Jams, miscellaneous, average	1 T.	25	303	0.4	75.0	0.1	—	3–9	10	0.01	0.02	—
Jellies, miscellaneous, average	1 T.	25	261	0.2	65.0	—	13	4	10	0.01	0.02	1
Corn oil	1 T.	11	99	—	—	100.0	—	—	—	—	—	—
Cottonseed oil	1 T.	11	99	—	—	100.0	—	—	—	—	—	—
Olive oil	1 T.	15	126	—	—	100.0	—	—	—	—	—	—
Peanut oil	1 T.	15	130	—	—	100.0	—	—	—	—	—	—
Margarine, salted	1 T.	15	103	0.6	0.4	81.0	624	936	56	—	—	—
Margarine, unsalted	1 T.	15	103	0.6	0.4	81.0	40	60	56	—	—	—
Peanut butter	1 T.	17	104	26.1	19.0	47.8	—	—	360	110	200	—

Symbols:
T. = teablespoon — = none present or insufficient data
t. = teaspoon

TABLE 107.—*Dietary Sources of Mineral Nutrients*

Calcium	Chlorine	Copper
*Milk *Cheese *Cream *Sardines Salmon Shellfish Egg yolk Prunes Raspberries Strawberries Oranges Figs *Beans *Broccoli *Kale *Turnip greens *Cauliflower Cabbage Carrots Lettuce Peas Turnips Bran Bread Almonds Filberts	*Foods cured with salt, such as ham or sauerkraut Beef, lean *Clams *Oysters Eggs *Cheese Buttermilk Milk Bananas Dates Raisins Cabbage Celery Lettuce Potatoes Spinach Tomatoes Turnip greens *Bread Molasses	*Liver Bacon *Shellfish Fish Duck Egg yolk Prunes *Mushrooms Leafy vegetables Legumes *Bran Bread Grain, whole or embryo Oatmeal *Nuts Yeast
Iodine	**Iron**	**Magnesium**
*Fish *Cod liver oil *Seafood *Iodized salt Vegetables, cereals, dairy products, and fruits produced on soils which are good in iodine content	*Liver *Beef heart *Kidney Meat *Clams *Oysters Fish Shrimp *Egg yolk *Apricots Bananas Dates Figs Prunes Raisins *Beans *Beet greens *Chard *Peas *Soy beans *Turnip greens *Lentils Asparagus Beets Broccoli Brussels sprouts Mushrooms Parsnips Potatoes Spinach *Tomatoes *Bran *Bread enriched white Oatmeal Whole grains Molasses	*Beef *Clams Fish Oysters Cheese Milk *Prunes Raisins Bananas Dates Figs Raspberries *Beans *Brussels sprouts *Chard *Corn *Peas *Spinach Beets Cabbage Carrots Celery Kale Parsnips Potatoes Turnip greens *Bran *Oatmeal *Whole grains *Nuts Macaroni

* This food is especially rich in this element.

TABLE 107.—*Continued*

Manganese	Phosphorus	Potassium
*Liver *Pancreas Oysters *Bananas *Dates Raspberries Rhubarb *Beans *Beets *Celery *Cucmbers *Onions *Peas Carrots Eggplant Leafy vegetables Peppers Tomatoes *Bran *Oatmeal Whole grains Nuts	*Liver *Meat *Fish *Shellfish *Eggs *Cheese *Milk Cream Prunes *Beans, dried *Peas Beans, green Cauliflower Corn Kale Potatoes Turnip greens *Bran *Grains, whole or embryo *Oatmeal Bread Peanuts *Yeast	*Liver *Meat *Fish *Seafood *Eggs *Cheese *Milk *Prunes *Raisins Bananas Cherries Dates Figs Grapes Peaches Pears Pineapples Rhubarb Strawberries *Corn *Legumes Beets Carrots Celery Cucumbers Green, leafy vegetables Onions Potatoes Spinach Tomatoes Turnips *Bran *Oatmeal *Whole grains *Nuts *Macaroni *Yeast

Sodium	Sulfur	Zinc
*Beef *Clams *Oysters Eggs *Cheese Milk Cantaloupes Prunes Pumpkins Raisins Beets Carrots Cauliflower Celery Kale Legumes Radishes Spinach Turnips *Bread *Crackers *Wheat germ Whole grains Bran Oatmeal Nuts *Blood	*Meat, lean *Fish *Shellfish *Eggs *Cheese Milk Dates Figs *Legumes Broccoli Brussels sprouts Cabbage Corn Kale Onions Potatoes Rutabaga Spinach Water cress *Bran *Oatmeal Bread Whole grains *Nuts *Cocoa *Yeast Chocolate Macaroni	*Liver *Pacreas *Oysters Fish Pineapples *Beans *Dandelions *Lentils *Peas *Spinach *Water cress Beets Broccoli Cabbage Carrots Potatoes

* This food is especially rich in this element.

TABLE 108. *Fruits and Vegetables, Classified as to Carbohydrate Content*[1314]

Group 1 (3 per cent carbohydrate)

Asparagus, fresh
Asparagus, canned, including sieved
Asparagus-bean sprouts, fresh
Bamboo shoots, fresh
Beans, green and wax, canned, including sieved
Bean sprouts (from mung beans), fresh
Beet greens, fresh
Broccoli, fresh
Cabbage, fresh
Cabbage, Chinese, fresh
Cauliflower, fresh
Cauliflower, canned
Celery, fresh
Celery, canned and sieved
Chard, fresh
Chicory, leaves, fresh
Cornsalad, fresh
Cress, garden, fresh
Cucumbers, fresh
Dock, fresh
Endive, fresh
Escarole, fresh
Fennel, fresh
"French endive," fresh
Lettuce, fresh
Mustard greens, fresh
Orach, garden, fresh
Orach, Peruvian, fresh
Pokeberry or poke shoots, fresh
Purslane, fresh
Quinoa, fresh
Radishes, fresh
Rhubarb, fresh
Rhubarb, canned, w.p.
Rutabaga tops, fresh
Sauerkraut, fresh
Sauerkraut, canned
Seakale, fresh
Sorrel, fresh
Spinach, fresh
Spinach, canned, including sieved
Spinach, New Zealand, fresh
Squash, summer, fresh
Taro shoots, fresh
Tomatoes, fresh
Tomatoes, canned
Tomato juice, fresh
Tomato juice, canned
Turnip tops, fresh
Udo shoots, fresh
Vegetable marrow, fresh
Vine spinach, fresh
Water cress, fresh

Group 2 (6 per cent carbohydrate)

Amaranth, fresh
Beans, hyacinth-bean, pods, fresh
Beans, scarlet runner, green pods
Beans, snap, green, and wax, fresh
Blackberries, canned, w.p.
Borage, fresh
Cantaloupe
Carrots, canned, including sieved
Celery root or celeriac, fresh
Chives, fresh
Collards, fresh
Dandelion greens, fresh
Eggplant, fresh
Gooseberries, canned, w.p.
Jew's mallow, fresh
Kale, fresh
Kohlrabi, fresh
Lambsquarters, fresh
Leeks, fresh
Melons, honeydew, casaba, and Spanish, fresh
Muskmelons, fresh
Nettle, fresh
Okra, fresh
Onions, Welsh, fresh
Palmetto or palmetto cabbage, fresh
Parsley, fresh
Peaches, canned, w.p.
Peppers, green and red, fresh
Pimientos, canned
Plums, excluding prunes, canned, w.p.
Pumpkin, fresh
Pumpkin and squash, canned
Salad-rocket, fresh
Soy beans, green, shelled, fresh

1314. CHATFIELD, C. and ADAMS, G.: U. S. Dep't Agriculture, Circular No. 59, 1940.

TABLE 108.—*Continued*

Group 2—*Continued*

Soy bean sprouts, fresh
Squash, cushaw, fresh
Squash, winter, fresh
Strawberries, fresh
Strawberries, canned, w.p. and j.p.
Strawberry juice, fresh
Sweet potato tops, fresh
Taro, leaves and stems, fresh
Turnips, fresh
Watermelon, fresh

Group 3 (9 per cent carbohydrate)

Applesauce, canned, unsweetened
Apricots, canned, w.p.
Artichokes, globe or French, fresh
Asparagus-beans, pods, fresh
Beets, fresh
Beets, canned, including sieved
Blackberries, fresh
Blackberries, canned, j.p.
Backberry juice, fresh
Blueberries, canned, w.p. and j.p.
Brussels sprouts, fresh
Cape gooseberry, fresh
Carrots, fresh
Cherries, red and white, canned, w.p.
Chervil, fresh
Cranberries, fresh
Currants, fresh
Currant juice, fresh
Ginger root, fresh
Gooseberries, fresh
Grapefruit, fresh
Grapefruit, canned, w.p. and j.p.
Grapefruit juice, fresh
Ground cherries, fresh
Lemons, fresh
Lemon juice, fresh
Lemon juice, canned
Limes, sweet, fresh
Lime juice, fresh
Loganberries, canned, w.p.
Loganberry juice, fresh
Onions, fresh
Oranges, mandarin type, fresh
Orange juice, mandarin type, fresh
Papayas, fresh
Parsley, fresh
Peaches, canned, j.p.
Pears, canned, w.p.
Peas, fresh (very young)
Peas, canned, including sieved
Peas, sugar peas, green pods, fresh
Prickly pear, fresh
Prunes, canned, w.p.
Quince juice, fresh
Raspberries, canned, w.p.
Rutabaga, fresh
Tangerines, fresh
Tangerine juice, fresh

Group 4 (12 per cent carbohydrate)

Apple juice, fresh
Applesauce, canned, j.p.
Apricots, fresh
Apricots, canned, j.p.
Apricots, canned, sieved, unsweetened
Beans, Lima, green, canned
Cherries, sour, fresh
Cherries, red and white, canned, j.p.
Crabapple juice, fresh
Figs, canned, w.p.
Grapefruit juice, canned, unsweetened
Grapes, canned, w.p.
Guavas, fresh
Kumquats, fresh
Lambsquarters, Algerian, fresh
Loganberries, fresh
Loganberries, canned, j.p.
Loquats, fresh
Mulberries, fresh
Oranges, fresh
Oranges, Seville or sour, fresh
Orange juice, fresh
Orange juice, canned
Peaches, fresh
Peaches, canned, sieved, unsweetened
Peach juice, fresh
Pears, canned, j.p.
Pineapple, fresh
Pineapple, canned, w.p.

TABLE 108.—*Continued*

Group 4—*Continued*

Pineapple, juice, fresh
Pineapple juice, canned
Plums, excluding prunes, fresh
Quinces, fresh
Raspberries, fresh
Raspberries, canned, j.p.
Raspberry juice, fresh
Rose apple, fresh
Soy beans, dry seeds
Surinam cherry or pitanga, fresh

Group 5 (15 per cent carbohydrate)

Apples, fresh
Beans, broadbeans, green, shelled
Beans, red kidney, canned
Black salsify, fresh
Blueberries, fresh
Blueberry juice, fresh
Cherries, black, canned, w.p.
Corn, fresh (very young)
Grapes, fresh
Huckleberries, fresh
Huckleberry juice, fresh
Jerusalem artichokes, tubers, fresh
Mangoes, fresh
Nectarines, fresh
Onions, top onions, fresh
Papaws, fresh
Parsnips, fresh
Pears, fresh
Peas, fresh (medium mature)
Pineapple, canned, j.p.
Salsify, fresh
Shallot, fresh
Vegetable oyster or salsify, fresh

Group 6 (18 per cent carbohydrate)

Beans, baked, canned
Carissa or Natal plum, fresh
Chayote roots, fresh
Cherries, sweet, fresh
Cherries, black, canned, j.p.
Corn, sweet, canned
Crabapples, fresh
Figs, fresh
Garlic, fresh
Grape juice, fresh or bottled
Haws, scarlet, fresh
Horse-radish, fresh
Passion fruit, fresh
Persimmons, Japanese
Pomegranates, fresh
Potatoes, fresh
Prunes, canned, j.p.
Prune juice, canned
Sapodilla, fresh
Sapota, fresh
Waternut, tuber, fresh

Miscellaneous group (high carbohydrate)

Apples, dried
Apricots, dried
Asparagus beans, dry
Bananas, fresh
Bananas, dried
Beans, broadbeans, dry
Beans, kidney or common, dry
Beans, Lima, fresh
Beans, Lima, dry
Beans, mung, dry
Black-eyed peas, dry
Burdock, fresh
Cherries, maraschino, canned
Chick-peas, dry
Corn, fresh (medium mature and old)
Corn, dry, sweet, and field
Cowpeas, fresh, green, shelled
Cowpeas, dry
Currants, dried
Dasheen, tubers, fresh
Dates, fresh and dried
Figs, dried
Fruits canned in syrup (all kinds)
Garbanzo peas, dry
Jujubes, fresh and dried
Lentil, dry, whole and split
Litchi fruit, dried
Marmalade, plum, fresh
Peaches, dried
Pears, dried
Peas, fresh (mature)
Peas, dry, whole and split
Persimmons, native, fresh
Plantain, or baking banana, fresh
Prunes, fresh
Prunes, canned, sieved
Prunes, dried
Raisins
Sapote, fresh
Sugar-apple, fresh
Sweet potatoes, fresh
Sweet potatoes, canned
Sweetsop, fresh
Taro, tubers, fresh
Tomato catsup
Yams, fresh

ELIMINATION DIETS (ACCORDING TO ROWE)[643]

TABLE 109.—*Elimination Diet 1*

FOODS ALLOWED

Tapioca
Rice

Rice biscuit
Rice bread

Lettuce
Chard
Spinach
Carrots
Sweet potato
Yam

Lemon
Grapefruit
Pears

Lamb

Sugar
Salt
Sesame oil
Olive oil
Gelatin, plain

Lime- and lemon-flavored gelatin
Maple syrup or syrup made with cane sugar flavored with maple

Lemon extract
Vanilla extract
Royal baking powder
Cream of tartar
Baking soda

SUGGESTED MENU

BREAKFAST

	Approximate amounts
Beverage	
(a) Grapefruit juice or lemonade with sugar added as desired. May be hot or cold.	½ cup
(b) Pear juice flavored with lemon.	½ cup
Cereal or cereal substitute	
(a) Boiled brown or polished rice served with hot pear juice, maple syrup, or syrup made from cane sugar flavored with maple.	½ cup
(b) Rice flakes, Rice Krispies, or puffed rice served with pears and pear juice and sugar.	¾ cup
(c) Tapioca cooked in water and sugar, with caramelized sugar or with lemon juice and grated lemon rind and sugar.	½ cup
Meat	
(a) Lamb chops or lamb patties.	1 med.
(b) Lamb tongue served hot or cold.	3 slices
(c) Lamb liver fried in sesame oil.	2 slices
Bread	
(a) Rice biscuits.	1 biscuit
(b) Rice bread.	2 slices
Butter substitute	
Sesame or olive oil with salt, jams, and jellies of specified fruits or maple syrup may be used on the bread.	
Jams or preserves	
(a) Lemon, grapefruit or carrot marmalade.	2 tsp.
(b) Pear butter.	2 tsp.
Fruit	
(a) Sectioned or half large grapefruit, fresh or canned, with sugar.	¾ cup
(b) Fresh or canned pears.	2 halves
This meal contains approximately 747 calories.	

TABLE 109.—*Continued*

LUNCH OR DINNER

	Approximate amounts
Soup	
Lamb broth, clear or with tapioca, rice, and carrots added. No pepper, spices, flavors, and no canned soup.	1 cup
Salad	
(a) Hearts of lettuce with sesame or olive oil and lemon juice dressing.	¼ head 1 tbsp. oil
(b) Vegetable salad of lettuce, chopped tender spinach leaves, and diced cooked carrots. Serve with sesame or olive oil and lemon juice.	½ cup veg. 1 tbsp.
(c) Sectioned grapefruit or halves of pears on shredded lettuce.	½ pear
(d) Grated raw carrot, sectioned grapefruit, or halves of pears molded in lime- or lemon-flavored gelatin.	½ cup
Meat	
(a) Lamb roast and chops.	2 med. chops
(b) Stew made of lamb, rice, and carrots. Thicken gravy with rice flour.	1 cup
(c) Lamb kidney, liver, and boiled tongue.	3 slices
Vegetables	
(a) Boiled brown or polished rice. Cold cooked rice may be fried in sesame oil.	½ cup
(b) Baked, boiled, or candied sweet potatoes or yams. Use sesame oil and brown sugar or maple syrup to candy the sweet potatoes.	1 med.
(c) Steamed spinach, chard, or carrots. Flavor with salt and sesame oil.	3 tbsp.
Bread	
Rice bread or rice biscuit.	2 slices
Butter substitute	
As suggested for breakfast.	1 tbsp.
Jams, preserves, or jellies	
Choice of those suggested for breakfast.	2 tsp.
Desserts	
(a) Pears baked with maple syrup or brown sugar.	1 whole pear
(b) Rice cupcakes or rice cookies.	1 cake
(c) Lemon- or lime-flavored gelatin, plain, whipped, or with grapefruit or pears.	½ cup
(d) Tapioca flavored with caramel or lemon juice and lemon rind and sugar.	½ cup
(e) Rice pudding flavored with lemon juice and rind, served with lemon sauce.	½ cup
(f) Lemon water ice made at home. (Commercial ices or sherberts contain milk or eggs.)	
Beverage	
(a) Grapefruit juice or lemonade with sugar.	1 cup
(b) Pear juice.	1 cup
Candies	
(a) Candied lemon or grapefruit peel.	3 slices
(b) Puffed rice candy or marshmallows made at home.	2 pieces
(c) Maple sugar candy, pure.	
(d) Fondant.	

This menu contains approximately 1,328 calories. Total for the day, 3,403 calories.

Carbohydrate	336 Gm.	Ca	0.350 Gm.
Protein	132 "	P	1.359 "
Fat	170 "	Fe	0.207 "

TABLE 110.—*Elimination Diet 2*

FOODS ALLOWED

Corn
Rye

Corn pone
Corn-rye muffin
Rye bread
Ry-Krisp

Beets

Squash
Asparagus
Artichoke

Pineapple
Peach
Apricot
Prune

Chicken (no hens)
Bacon

Sugar

Salt
Mazola oil
Sesame oil

Gelatin, plain or flavored with pineapple
Karo corn syrup
Maple syrup or syrup made with cane sugar flavored with maple
White vinegar
Vanilla extract

Royal baking powder

Cream of tartar
Baking soda

SUGGESTED MENU

BREAKFAST

	Approximate amounts
Beverage	
(a) Pineapple or prune juice.	½ cup
(b) Apricot, peach, and pineapple juices mixed with sugar.	½ cup
Cereal	
(a) Cornflakes served with apricots, peaches, or prunes and juice and sugar.	1 cup 4 prunes
(b) Corn meal mush served hot with maple or Karo syrup.	½ cup
(c) Sliced cold corn meal mush fried in Mazola oil or bacon fat served with syrup and strips of bacon.	3 slices 4 strips
Meat	
(a) Bacon.	4 strips
(b) Chicken croquettes.	2
(c) Sautéed chicken livers with bacon.	3 tbsp.
Bread	
(a) Corn pone.	2 slices
(b) Corn and rye muffins.	2 muffins
(c) Rye bread.	2 thin slices
(d) Ry-Krisp.	2 wafers
Butter substitute	
Mazola or sesame oil with salt, bacon grease, jams, preserves, or jellies of specified fruits or maple syrup may be used on the bread.	1 tbsp.
Jams, preserves, or jellies	
Peach, prune, apricot, or pineapple.	2 tsp.
Fruit	
(a) Fresh or canned pineapple, peaches, apricots, or prunes.	2 slices
(b) Stewed dried prunes. Do not used dried apricots or peaches.	4 prunes

This menu contains approximately 895 calories.

TABLE 110.—*Continued*

LUNCH OR DINNER

	Approximate amounts
Soup	
Chicken broth. (No pepper, seasonings and no canned or restaurant broth.)	½ cup
Salad	
(a) Any combination of artichoke hearts, beets, and asparagus with Mazola or sesame oil and white vinegar.	1 cup mixed veg. or equiv.
(b) Cold sliced beets marinated in white vinegar, seasoned with salt and sugar.	5 slices
(c) Any combination of pineapple, peaches, apricots, and prunes. Any of these fruits may be molded in plain or pineapple-flavored gelatin. Mazola oil, salt, and white vinegar may be used.	½ cup
Meat	
(a) Chicken-roasted, fried, broiled, or fricasseed. Use corn meal or rye flour for dredging and cornstarch for thickening gravy. Mazola oil, sesame oil, bacon or chicken fat can be used for frying.	½ fryer or equiv.
(b) Chicken croquettes.	2 med.
(c) Sautéed chicken livers.	½ cup
Vegetables	
(a) Fresh or canned beets, corn, squash, asparagus, and artichokes with salt and Mazola oil if desired.	½ cup
(b) Hominy.	½ cup
Bread	
(a) Choice of those suggested for breakfast.	
(b) Corn crisps; served with salad or soup.	2
Butter substitute	
As suggested for breakfast.	1 tbsp.
Jams, preserves, or jellies	
Choice of those suggested for breakfast.	2 tsp.
Desserts	
(a) Fruits as suggested for breakfast.	
(b) Rye coffee cake.	2 cookies
(c) Cornstarch pudding with crushed fruit.	½ cup
(d) Jellied prunes and pineapple.	4 prunes
(e) Plain or pineapple-flavored gelatin with fruits listed in this diet.	½ cup
Beverage	
Choice of those suggested for breakfast.	
Candies	
(a) Candied pineapple.	1 slice
(b) Dried pitted prunes stuffed with candied pineapple or vanilla-flavored fondant.	2 prunes

This menu contains approximately 1,036 calories.
Total for the day: calories 2,968.

Carbohydrate	322 Gm.	Ca	0.290 Gm.
Protein	89 "	P	1.401 "
Fat	147 "	Fe	0.019 "

TABLE 111.—*Elimination Diet 3*

FOODS ALLOWED

Tapioca
White potato

Soy-Lima-potato bread
Soy-potato bread or muffins

Beef
Bacon

Tomato
Carrots

Lima beans
Soy beans
String beans
Peas

Lemons
Grapefruit
Peaches
Apricots

Sugar
Salt

Sesame oil
Soy bean oil
Gelatin, plain
Lime- or lemon-flavored gelatin
Maple syrup or syrup made with cane sugar flavored with maple
Vanilla extract
Lemon extract
Royal baking powder
Baking soda
Cream of tartar

SUGGESTED MENU

BREAKFAST

	Approximate amounts
Beverage	
(a) Grapefruit juice or lemonade with sugar as desired.	½ cup
(b) Tomato juice.	½ cup
Cereal substitute	
(a) Tapioca cooked with apricot or peach juice or with puréed fruit and sugar.	½ cup
(b) Tapioca cooked in water, sweetened with sugar and flavored with lemon juice and grated lemon rind, caramel, brown sugar, or maple syrup.	½ cup
(c) During the war, if tapioca is unavailable, (1) white potato must be served (see lunch menu) or (2) soy-potato pudding may be used.	
Meat	
(a) Bacon.	4 slices
(b) Beefsteak or beef patties.	2 med. pats.
(c) Calves' or beef liver and bacon.	2 slices
(d) Boiled beef tongue, cooked plain.	2 slices
(Hashed brown potatoes cooked in prescribed oils can be served with meats.)	½ cup
Bread	
(a) Soy bean-potato or soy-Lima-potato breads.	2 slices
(b) Soy-Lima-potato muffins.	2 muffins
(c) Soy bean pancakes served with maple syrup or syrup made of cane sugar flavored with maple.	4 med.
Butter substitute	
Sesame or soy bean oil with salt, bacon grease, jams, preserves, jellies, or maple syrup may be used on bread.	1 tbsp.
Jams or preserves	
(a) Lemon, grapefruit, or carrot marmalade.	2 tsp.
(b) Peach or apricot jam.	2 tsp.
(c) Tomato preserves flavored with lemon.	2 tsp.
Fruit	
(a) Fresh or canned grapefruit with sugar.	½ grapefruit
(b) Peaches or apricots (fresh or canned).	1 peach or 3 apricots
(c) Sliced tomatoes with sugar.	

This menu contains approximately 656 calories.

Table 111.—*Continued*

Lunch or Dinner

	Approximate amounts
Soup	
(a) Beef broth clear (not canned) or with tapioca, carrots, tomatoes, Lima beans, or peas (no pepper).	½ cup
(b) Lima bean soup flavored with bacon.	½ cup
(c) Vegetable broth made with tomatoes, carrots, Lima beans, string beans, and diced potatoes.	½ cup
Salad	
(a) Vegetable salad of any combination of tomatoes, carrots, Lima beans, string beans, and peas. Serve with sesame or soy oil, lemon juice, and salt.	½ cup
(b) Fruit salad of grapefruit, peaches, and apricots. (Use lemon- or lime-flavored gelatin with any of the listed fruits or vegetables. Cut tender young carrots into long thin strips and place in iced salted water for one-half hour. Use as a garnish for salads or as an appetizer.)	¾ cup
Meat	
(a) Beef served as steak, roast, patties, or meat loaf.	Liberal serving of meat
(b) Beef stew with white potatoes, carrots, tomatoes, peas, Lima beans, or string beans. Thicken gravy with potato starch.	
(c) Calves' or beef liver and bacon.	3 slices
(d) Boiled calves' or beef tongue, cooked plain.	3 slices
Vegetables	
(a) White potatoes may be baked, boiled, riced, hash browned, or French fried, salted to taste. Use only sesame or soy bean oil.	1 med.
(b) Fresh or canned tomatoes, carrots, lima beans, string beans, peas, or soy beans.	½ cup
Bread	
Choice of those suggested for breakfast.	
Butter substitute	
As suggested for breakfast.	1 tbsp.
Jams, preserves, or jellies	
Choice of those suggested for breakfast.	2 tsp.
Dessert	
(a) Fruit as suggested for breakfast.	
(b) Tapioca pudding made with apricots or peaches.	½ cup
(c) Soy-potato starch pudding.	
(d) Lemon or apricot waterice made at home.	½ cup
(e) Soy or soy-potato cookies or cup cakes.	2 cookies
Beverage	
(a) Grapefruit juice or lemonade with sugar if desired.	½ cup
(b) Tomato juice.	½ cup
Candies	
(a) Candied grapefruit or lemon peel.	2 slices
(b) Fondant flavored with vanilla, lemon, or apricot.	2 slices
(c) Pure maple sugar candy.	

This menu contains approximately 1,267 calories.

Total for the day: Calories 3,190.

Carbohydrate	330 Gm.	Ca	0.300 Gm.
Protein	105 "	P	1.203 "
Fat	161 "	Fe	0.024 "

TABLE 112.—*Do's and Don'ts for Vitamin Conservation*

DO'S	DON'TS
Use as little water as possible in boiling foods.	Don't let cooked food stand.
Bring to a boil as quickly as possible.	Don't cook too much food at a time.
Plunge frozen foods into boiling water while still frozen.	Don't reheat foods unless necessary.
Serve raw frozen foods as soon as they have thawed.	Don't put foods through a sieve while they are still hot.
Prepare fruits and vegetables for salads immediately before serving.	Don't use soda in cooking green vegetables.
Prepare fruits and vegetables just before cooking.	Don't fry, roast, or stew foods if they can be boiled. Boiling is less destructive of vitamin A, thiamine, and ascorbic acid.
Use pot liquor from boiled vegetables for soups, gravies, and sauces.	
Stir foods as gently and as little as possible while cooking to avoid admixture of air.	
Keep foods tightly covered and stored at low temperatures.	

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